INDEX NUMBER

VOL. CLXXXI, No. 6 JUNE, 1931 No. 711

JUN 5 1931

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JUNE, 1931

ORIGINAL ARTICLES.

IODIN IN EXOPHTHALMIC GOITER.

A COMPARISON OF THE EFFECT OF ETHYL IODID AND POTASSIUM IODID WITH THAT OF LUGOL'S SOLUTION.

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SINCE the introduction of iodin in the form of Lugol's solution in the treatment of exophthalmic goiter by Plummer, in 1923, there has been considerable speculation as to the nature of the response which iodin characteristically produces in that disease. In a previous study[1] from this clinic, the matter of range of effective dosage was considered. In Boston, a nongoitrous region, at least it was found that in most patients with exophthalmic goiter 1 drop of Lugol's solution per day by mouth causes as great a fall in the basal metabolic rate as do much larger doses. The present study attempts to determine whether the type of iodin compound or the route of entry into the body are factors in the iodin response. For this purpose the effect of ethyl iodid *via* the lungs and of potassium iodid *via* the mouth has been compared with that of Lugol's solution *via* the mouth.

In 1920 Neisser[2] reported clinical improvement in several cases of exophthalmic goiter on small doses of potassium iodid. He started with a 5 per cent solution, 2 to 5 drops three times a day and increased 1 drop at a time to 8 to 20 drops. A year later E. and M. Mellanby[3] reported that iodin, when given either in the form of cod-liver oil or in small doses of potassium iodid, caused a striking improvement in symptoms, preceded by a period of aggravation of symptoms and increased metabolism. In the same year Loewy and Zondek[4] confirmed the clinical results of Neisser and checked them with metabolic rate determinations in 3 cases. Following this there were several reports on the treatment of exophthalmic goiter by this method. In 1924 Cowell and Mellanby[5] reported a detailed study of 8 cases treated with potassium iodid in doses varying from 1 to 18 grains. They found distinct clinical improvement in all cases. The lowering of the basal metabolic rate and slowing of the pulse rate was maximum between the tenth and twentieth days of treatment.

With the introduction of Lugol's solution, the use of potassium iodid in the treatment of exophthalmic goiter was generally abandoned. In 1926 Fitzgerald[6] reported that resublimed iodin in solution in dilute hydriodic acid was as effective in lowering the pre-operative basal metabolic rate as Lugol's solution. There have been several reports on the use of a combination of an iodin compound and vitamins A and D. Adamson and Cameron[7] showed in a series of 12 cases that "vitiodum" (a combination of vitamins A and D and iodized jecoleic acid) is as effective as Lugol's solution when administered in exophthalmic goiter, and the limits of its beneficial action closely resemble those of Lugol's solution. In a later report Fraser and Cameron[8] demonstrated in a study of 4 cases that a combination of vitamins A and D and sodium iodid produces the same beneficial effect as "vitiodum" and as Lugol's solution in the pre-operative treatment of exophthalmic goiter. They further showed that the vitamins alone are ineffective. At the same time Rabinowitch[9] also reported on the use of "vitiodum" in exophthalmic goiter. He showed that in 12 cases of exophthalmic goiter treated with this mixture of iodized fatty acid and vitamins the average decrease in basal metabolic rate was 4.7 per cent per day, whereas in another group of 12 cases, clinically similar, treated with Lugol's solution the average fall was 3.2 per cent per day. These results were obtained in spite of the smaller dose of available iodin given with the vitamin-containing mixture than when Lugol's solution was used. Recently Fulton and Alt,[10] in a study of 42 bed patients at the Peter Bent Brigham Hospital, showed that Lugol's solution, sajodin—calcium iodobehenate, $Ca(C_{21}H_{42}ICOO)_2$ and saturated potassium iodid solution are equally effective in the pre-operative treatment of thyrotoxicosis as judged from the rate of reduction in the basal metabolism. In 15 cases treated with

Lugol's solution the average daily fall in basal metabolic rate was 3.2 per cent, in 11 cases receiving sajodin it was 3 per cent and in 16 receiving saturated solution of potassium iodid it was 3.3 per cent.

A few observations on the action of ethyl iodid were made in this clinic several years ago at a time when the substance was being used in the determination of cardiac output by the Henderson and Haggard method. It was thought that a volatile agent administered *via* the lungs might have a prompter action than one administered orally. The observations made showed that ethyl iodid produced the characteristic response, but pressure of other work prevented a systematic study of it at that time.

The recent development of a convenient technique for the administration of ethyl iodid in the treatment of fungus infections of the skin by Swartz, Blumgart and Altschule[11] revived our interest in this drug, and in consequence the present series of observations were made.

Method. The patients were kept at rest in bed in the hospital and daily basal metabolic rates obtained. After the metabolism had reached a level on rest alone iodin administration was begun. Ethyl iodid was administered *via* the respiratory tract by having the patient breath through the inhalator described by Swartz, Blumgart and Altschule.[11] In the first 5 cases 2 gm. (1 cc.) were given daily in one dose; in the remainder the dosage was 4 gm. (2 cc.) daily.* The inhalations occupied a period of about twenty minutes. At this rate of administration no toxic effects were noted. If given more rapidly the patient became dizzy and slightly stuporous. In a few cases salivation was marked during the inhalation.

The inhalations were continued until the metabolism again reached a level. Lugol's solution, 2 cc. (30 minims) or 250 mg. daily by mouth, was then substituted and continued for three days or more, followed by a subtotal thyroidectomy.

A similar procedure was followed in those cases treated with potassium iodid. After a resting level of metabolism was obtained potassium iodid in the form of saturated solution was given by mouth until a level of metabolism was again reached. The first 3 patients received 3 grains (0.18 gm.) daily, the remainder received 6 grains (0.36 gm.), or 275 mg., daily.

Material. A total of 25 patients were treated with ethyl iodid for a period varying from seven to fifteen days. One of them is excluded from the following analysis because she developed pneumonia and the inhalations had to be discontinued.

The results in 24 cases are summarized in Table I and Chart I. Chart II illustrates a typical response to ethyl iodid.

* According to the results obtained by Blumgart, Gilligan and Swartz[15] about 46 per cent of the ethyl iodid is retained in the body. This is equivalent to 1470 mg. iodin.

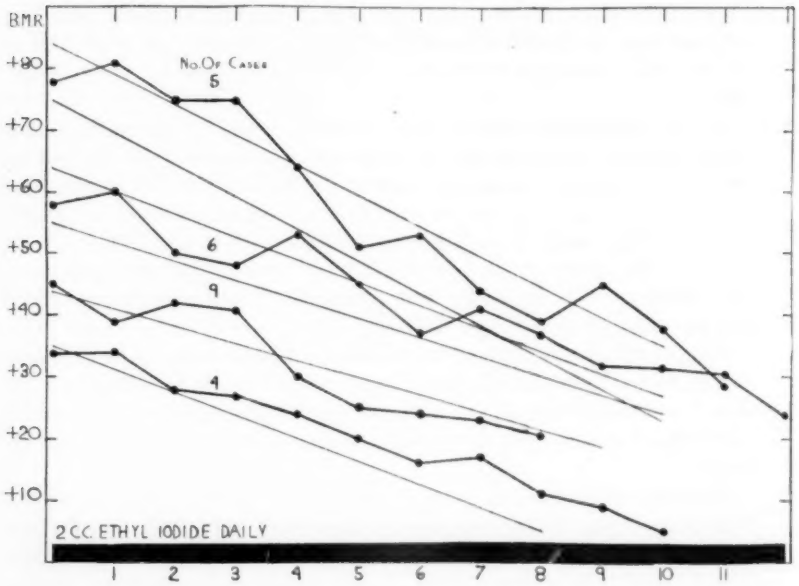

CHART I.—Comparison of the metabolic rate changes produced by ethyl iodid and Lugol's solution[12] in exophthalmic goiter. The cases were grouped in accordance with the resting levels, each 10 point interval constituting a group.

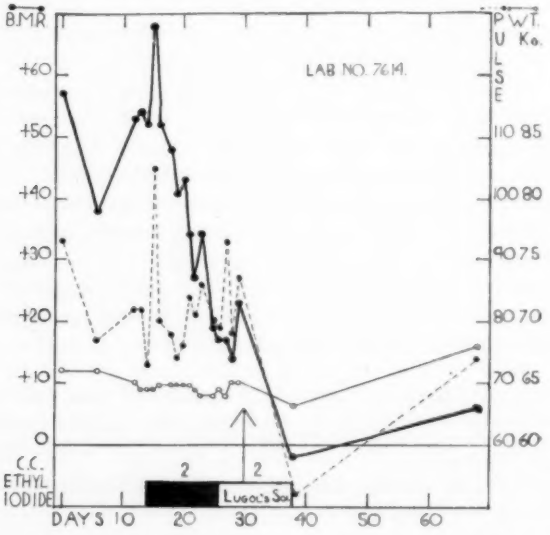

CHART II.—Reduction in basal metabolism of a patient with exophthalmic goiter as a result of the pre-operative administration of ethyl iodid. Lugol's solution did not produce any further response.

TABLE 1.—ANALYSIS OF THE SUCCESSIVE EFFECTS OF REST, ETHYL IODID AND LUGOL'S SOLUTION.

Laboratory No.	Age.	Initial BMR in hospital.	Time at rest before treatment days.	Average resting level BMR.	Ethyl iodid, 2 cc. daily.															Average level of BMR.	Day fall began.	Time for maximum change.	Change in BMR.	Maximum daily fall.	Lugol's sol. 2 cc. daily		
					1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16+						Average level BMR.	Number days observed.	Change in BMR.
		%		%																	%					%		
7795	36	+28	3	+28	....	+21	+18	+23	+15	+ 3	+11	....	+ 6*	+ 4	+ 9	....	....	....	....	....	+ 7	1-2	6	−21	−3.5	+ 7	2	0
7675	25	+18	5	+32	+10	+15	+22	+23	+15	....	+ 9	+ 7	0	− 6	....	− 4	....	0	....	....	− 5	1	10	−37	−3.7	− 2	3	+ 3
7904	30	+34	5	+38	+50	....	+32	....	+32	+28	....	+20	+13	+ 5	....	+ 7	+ 5	+ 9	+ 5	....	+ 6	3	10	−32	−3.2	+ 6	3	0
7559	26	+60	7	+38	+43	+47	+37	+26	+17	....	+32	+ 7	+14	+14*	+ 9	....	....	+ 4	+14	+13	+12	4	8	−26	−3.3	+10	9	− 2
7401	37	+41	3	+40	+34	....	+36	+21	+31	+28	+20	+25	+29*	....	+18	+13	....	....	....	(19th day)	+23	1	4	−17	−4.3	+16	3	− 7
7816	17	+56	8	+46	+36	+38	+37	+15	+11	....	+10	+10	+ 7*	− 1	....	....	....	....	....	....	+ 9	1	5	−37	−7.4	− 1	1	−10
7490	37	+59	3	+45	....	+45	+41	+36	+29	+37	+34	....	+32	+35*	....	+27	+31	+35	....	+25	+33	3	5	−12	−2.4	+30	6	+ 3
7483	36	+59	5	+46	....	+39	+60	+41	+20	+16	+19*	....	+20	....	....	+15	....	+19	....	+30	+17	2	6	−29	−4.8	+22	12	+ 5†
7640	59	+50	5	+46	+46	+53	+39	....	+27	+36	+19	+18	+18*	+19	....	+26	....	....	....	(20th +24)	+18	3	7	−28	−4.0	+23	3	+ 5
7749	67	+53	9	+44	+35	+48	....	+24	+24	+30	+25**	....	....	....	....	....	....	....	....	....	+26	1	4	−18	−4.5			
7797	37	+44	4	+47	+41	....	+34	+39	+27	+21	+27	+16	....	+13	+19	+ 9*	+15	....	....	....	+14	1	10	−33	−3.3	+15	1	+ 1
7882	33	+40	5	+42	+41	+32	+48	+32	+34	....	+30	+24	....	+31	....	+25*	....	+29	....	....	+27	2	8	−15	−1.9	+29	1	+ 2
7899	50	+47	5	+44	+38	+36	+30	....	+25	....	+24	+25	+34	+24	+18	+12	....	....	....	....	+27	1	5	−17	−3.4	+15	3	−12‡
7549	21	+53	3	+52	+52	+51	+41	....	+37	+29	+25	+28	+23	+19	....	+14	+ 1	+11	+16*	+15	+ 9	3	13	−43	−3.3	+13	4	+ 4
7614	46	+53	3	+53	+68	+52	....	+48	+41	+43	+34	+27	+34	....	+19	+17*	+17	+14	+23	(19th day)	+18	4	11	−35	−3.2	+18	3	0
7666	28	+59	4	+59	+55	+55	+55	....	+51	+49	+49*	+50	+45	+50	....	....	....	....	....	....	+50	1	5	− 9	−1.8	+48	3	− 2
7944	26	+74	5	+62	+52	+40	+35	+36	....	+32	....	+49	+26	+29*	+19	....	....	....	....	....	+28	1	9	−34	−3.8	+19	1	− 9
7870	40	+80	7	+62	+60	+55	+58	+55	+52	....	+53	+35	+42	+35	....	+38*	....	+36	....	....	+36	2	8	−26	−3.3	+36	2	0
7477	42	+68	5	+61	+70	....	+59	+72	+49	+44	+50	+45	+	+41	+40*	....	+39	+36	+28	(17th	+41	5	6	−20	−3.3	+37	6	− 4
7421	44	+67	4	+70	+84	+74	....	+53	+31	....	+39	+32	+26	....	+20	+23*	+18	+12	....	+43)	+22	3-4	11	−48	−4.4	+15	2	− 7
7906	39	+73	2	+70	....	+69	....	+57	+55	+44	+40	....	+48	+44	+34	+35	+41*	+47	....	+37	+37	3-4	11	−33	−3.0	+42	3	+ 5
7358	23	+93	5	+70	+77	+70	+62	+50	+48	....	+50	+37	+39	+39*	+36*	....	....	....	....	....	+38	3	8	−32	−4.0	+36	1	− 2
6020	30	+75	3	+84	+82	+78	+79	+84	+52	....	+45	+49	+41	+28	+29*	+35	....	....	....	....	+29	2	10	−55	−5.5	+35	1	+ 6
7778	23	+92	2	+93	....	+82	+85	+77	+68	+61	....	....	+70*	+65	+41	+43	....	....	....	....	+66	1-2	6	−27	−4.5	+42	3	−24
Average:	All cases (24)	+57	4.6	+53																	+24.5		7.8	−28.5	−3.7			
	(23) Responding	+57	4.6	+53																	+23.4		7.9	−29.3	−3.8	+21.0	3.3	−2.2
	(23) with Lugol's	+57	4.4	+53																	+24.4		7.9	−29.0	−3.7	+22.2	3.3	−2.2

* Time when Lugol's solution was substituted for ethyl iodid.
** No Lugol's solution.
† Delayed by upper respiratory infection.
‡ Diarrhea during test period.

In 23 of the 24 cases there was a reduction of more than 10 points in the level of metabolism, the drop varying from 12 to 55 points. The paient who failed to make a maximum response had been receiving Lugol's solution for three weeks until ten days before entry into the hospital.

The average basal metabolism just after admission to the hospital was +57. After a resting period varying from two to nine days the average basal metabolism was +24. The average daily fall in metabolism was 3.7 points, varying from 1.8 to 7.4.

In 23 patients the effect of Lugol's solution in large doses was observed for an average period of 3.3 days following the period of ethyl iodid inhalation. Eleven dropped 1 to 26 points, 4 showed no change and 8 rose 1 to 6 points. Only 3 patients dropped 10 points or more. One of these developed diarrhea during the period of ethyl iodid inhalation, which subsided coincident with the substitution of Lugol's solution. The average basal metabolic rate after treatment with Lugol's solution was +22.

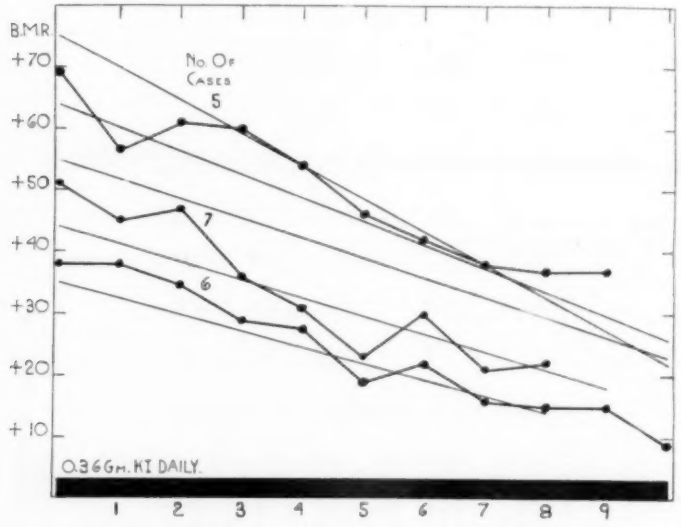

CHART III.—Comparison of the metabolic rate changes produced by potassium iodid and Lugol's solution[12] in exophthalmic goiter. The cases were grouped in accordance with the resting levels, each of the following intervals constituting a group: under 45, 45 to 59, 60 and over.

The fall began in one to five days. Fourteen patients showed a definite reduction in the first two days. In 5 instances it was delayed four to five days. The maximum response required seven to eight days, the variation being four to thirteen days. Fifteen patients, or 63 per cent, showed their maximum fall within eight days.

The data in Table I illustrate some of the peculiarities of the iodin response. In 7 cases there was a rise in metabolism on the first or the first and second days after ethyl iodid inhalations were begun. This rise has been noted previously, particularly as mentioned above, by E. and M. Mellanby.[3] In 13 cases the fall in metabolism had the characteristics of a "treppe" response. In the remaining cases the fall in the basal metabolic rate was uninterrupted but of varying rate.

TABLE 2.—ANALYSIS OF THE SUCCESSIVE EFFECTS OF REST, POTASSIUM IODID AND LUGOL'S SOLUTION.

Laboratory No.	Age, years.	First BMR in hospital.	Time at rest before Treatment days.	Resting level of BMR.	Potassium iodid 0.36 gm. daily.															Average level of BMR.	Time fall began, day	Time for maximum change.	Change in BMR.	Maximum daily fall.	Lugol's sol. 2 cc. daily		
					1	2	3	4	5	6	7	8	9	10	11	12	13	14	15						Average level BMR.	No. of days observed.	Change in BMR.
		%		%																%							
8105	21	+40	4	+27	....	+19	+20	+22	+14	+ 8	....	+ 4	+17	+ 7†	....	....	....	....	....	+ 9	1–2	6	−18	−3.0			
8041	64	+39	6	+34	+34	+34	....	+27	+22	+25	+11	+11*	+ 7	....	+13	....	....	....	....	+11	3–4	7	−23	−3.3	+10	3	− 1
8096	22	+53	3	+34	....	+35	+35	+31	+17	+22	+ 8	....	+11	+ 6†	....	....	....	....	....	+ 8	4	7	−28	−4.0			
7960	20	+83	6	+44	+36	....	+30	....	+22	+26	+20	+18	+15	+14*	....	+15	....	....	....	+15	1	9	−29	−3.2	+15	2	0
7971	34	+53	8	+44	+42	+45	+31	....	+13	+26	+14	+14*	....	+11	....	+ 1	....	....	....	+17	3	5	−27	−5.4	+ 6	4	−11
8127	27	+50	7	+44	+41	+41	....	+33	+26	+24	+27	+26	+18	....	....	+11	+11*	+ 9	+11	+11	4	12	−33	−2.8	+10	2	− 1
6397	26	+42	4	+46	....	....	+27	....	+23*	+15	....	....	....	....	....	....	....	....	....	+25	1–3	3	−21	−7.0	+15	1	−10
7185	43	+50	4	+49	+56	+46	+37	+34	....	+36	+32	+30*	+33	+15	+25	....	+16	....	....	+33	3	4	−16	−4.0	+19	5	−14
8128	32	+75	5	+46	+38	+39	+26	+38	....	+18	+15	+13	+19*	+12	+ 6	....	....	+14	+13	+16	1	6	−30	−5.0	+10	7	− 6
7990	35	+46	2	+53	+37	....	+32	+19	+ 3	+23	+ 9	+12	*	+10	....	....	....	....	....	+12	1	5	−41	−8.2	+10	1	− 2
7962	57	+69	8	+51	+41	+51	....	+35	....	+41	+23	+14	+23	+19*	+22	....	+16	....	....	+19	1	8	−32	−4.0	+19	3	0
6376	21	+81	6	+59	+53	....	+49	....	....	....	+27	+28	....	....	....	+26*	+26	....	....	+27	1	7	−32	−4.6	+26	1	− 1
7956	25	+85	5	+54	....	+51	+47	+31	+43	....	....	+34	+39	+37	+28	+21	....	+24	....	+37	3	4	−17	−4.3	+24	4	−13
7116	21	+70	7	+64	+52	+44	+53	+47	....	+36	+23*	+32	+33	+26	+32	....	+24	....	....	+23	1	7	−41	−5.9	+27	6	+ 4
6488	38	+97	7	+66	+59	+60	+55	....	+44	+44	+39	+37	+41	+40*	....	+44	+52	....	....	+39	1	7	−27	−3.9	+45	4	+ 6
8097	48	+52	9	+60	+59	+55	+51	+44	....	+35	+37	+35*	+37	+23	+34	....	....	....	....	+36	2	6	−24	−4.0	+31	3	− 5
7992	22	+78	5	+70	....	+62	+60	+64	....	+45	....	+38	+31	+49	+42	+39	+43	....	+40	+40	1–2	8	−30	−3.8	+40	2	0
8054	32	+108	3	+85	....	+83	+69	+59	+47	+50	+51	....	+38	+37*	+38	+26	....	....	....	+38	3	9	−47	−5.2	+26	2	−12
Average	All cases (18)	+65	5.5	+52																+23.1		6.7	−28.7	−4.5			
	(16) with Lugol's	+67	5.8	+54																+24.9		6.7	−29.4	−4.7	+20	3.1	−4.1

* Time when Lugol's solution was substituted for potassium iodid.
† No Lugol's solution.

Potassium Iodid. *Material.* Eighteen patients were treated with saturated solution of potassium iodid for a period of five to thirteen days. The results in these cases are summarized in Table II and in Chart III. Chart IV shows a typical response to potassium iodid.

All the patients responded with a fall in basal metabolic rate, varying from 16 to 47 points. The average basal metabolism soon after entry into the hospital was +65. After a rest period of two to nine days the metabolism was +52. At the end of the test period with potassium iodid it was +23, a drop of 29 points. The average daily reduction in metabolism was 4.5 points, varying from 2.8 to 8.2.

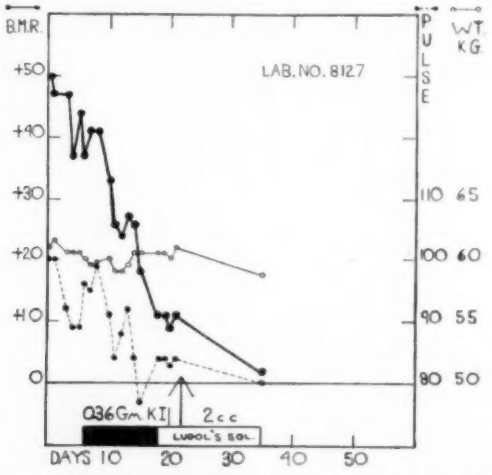

CHART IV.—Reduction in basal metabolism of a patient with exophthalmic goiter as a result of the pre-operative administration of potassium iodid. Lugol's solution did not produce any further response.

In 16 cases the effect of large doses of Lugol's solution was observed following the treatment with potassium iodid. The period of observation varied from one to seven days. Eleven showed a lowering of metabolism of 1 to 14 points, 2 showed a rise of 4 to 6 points and 3 showed no change. Five cases showed an appreciable reduction in basal metabolic rate of 10 points or more. The average reduction was 4.1 points.

The fall in metabolism began in one to four days. Seven cases showed an appreciable fall on the first day, 3 on the second day, 5 on the third day and 3 on the fourth day. The maximum response occurred in six and seven-tenths days. Three patients responded under five days, 5 on the fifth and sixth days, 7 on the seventh and eighth days, 2 on the ninth and 1 was delayed until the twelfth day. Thus, 83 per cent of the patients made their maximum response on potassium iodid within eight days.

The data of Table II show that only 1 case gave a rise in basal metabolic rate on the first day after the iodin medication was started. In 8 cases the drop in metabolism was characterized by "treppe."

Discussion. The response of exophthalmic goiter to ethyl iodid and to potassium iodid is essentially similar to the response to Lugol's solution. Charts I and III show this graphically. Here

our results are compared with those given by Means, Thompson and Thompson[12] which are based on a large series of patients treated with Lugol's solution. Our curves were drawn from the averages for several patients which were grouped according to the average metabolic rates before medication. These curves, being similar to those of Means, Thompson and Thompson, possess the essential characteristic that their slopes vary according to the height of the initial metabolic rate.

Most of the data in the literature on the iodin response in exophthalmic goiter are not comparable to our own mainly because of the different methods of collecting the data and the different modes of analyzing it. On the other hand, the data given by Starr, Segall and Means[13] for 8 cases treated with large doses of Lugol's solution and by Thompson, Brailey, Thompson and Thorp[14] for 17 cases treated with 1 drop of Lugol's solution, all obtained in the same clinic and analyzed similarly, are comparable. The average metabolic rate of the former on the day of beginning iodin treatment was +51. On the tenth day afterward it was +14, giving a rate of drop of 3.7 points per day. These results, however, apply to their patients who made a satisfactory response to the iodin. If the patients who made a less satisfactory response were included the daily drop undoubtedly would be much smaller. The patients treated by Thompson and others[14] showed an average resting metabolic rate of +46 and +19 at the end of the period of iodin medication, a drop of 27 points. Of their 17 patients 2 did not respond.

TABLE III.—THE PERCENTAGE DISTRIBUTION OF THE REDUCTION IN BASAL METABOLIC RATE RESULTING FROM ETHYL IODID, POTASSIUM IODID AND LUGOL'S SOLUTION.

BMR—In points.	Ethyl iodid, 24 cases, per cent.	Potassium iodid, 18 cases, per cent.	Lugol's solution one drop, 17 cases, per cent.
0 to 9	4	..	12
10 to 19	21	17	6
20 to 29	29	38	41
30 to 39	33	28	23
40 to 49	8	17	18
50 to 59	4	..	..

The fall in metabolism of the 15 patients which made an adequate response was 31 points (from +50 to +19). The average rate of fall was 4.4 points daily. Assuming the time for the maximum response for the whole group to be the same (seven days), the rate of fall was 3.9 points per day. These results compare closely with our own for the cases treated with ethyl iodid and with potassium iodid—3.7 points and 4.5 points, respectively. In Table III the distribution of the fall in metabolic rate of the cases treated with ethyl iodid and with potassium iodid and of the 1-drop cases of Thompson and others[14] are compared. The figures show clearly that the potassium iodid and the 1-drop cases were similar. The

ethyl iodid cases showed slight differences, being higher in the 0 to 19 and 30 to 39 ranges and lower in the 20 to 29 and 40 to 59 ranges. This probably has no statistical significance on account of the relatively small number of cases.

It is difficult to account for the second fall in basal metabolism in some of the patients which received Lugol's solution after their test period with ethyl iodid or potassium iodid. It is undoubtedly true that a certain number of patients will have a slight progressive fall in metabolism if rest and iodin medication are continued. This may account for part of the change. In addition, some patients under one type of medication show abrupt changes in metabolism after a level has apparently been reached for several days. Consequently, Lugol's solution may have been started in some of our cases during one of these level periods before the maximum response on the test drug had been reached. Similar changes in metabolism also occurred in the cases of Thompson and others[14] when the iodin medication was changed from 1 drop of Lugol's solution to larger doses.

Not only the metabolism, but the other symptoms and signs of the thyrotoxic state showed changes during the period of ethyl iodid or potassium iodid administration. In general, it is our impression that the improvement in the thyrotoxicosis under the influence of these two drugs was as much as could have been expected on adequate doses of Lugol's solution.

The patients treated with ethyl iodid and with potassium iodid pre-operatively were followed through the postoperative period. On the whole, the convalescent period of each group was no different in respect to severity of reactions or number of complications than the average group treated with Lugol's solution alone. One of the patients treated with potassium iodid died at the conclusion of the operation. Roentgen ray examination, postmortem, showed an air embolus in the pulmonary artery. This death surely cannot be attributed to the type of medication.

In view of the findings of Blumgart, Gilligan and Swartz,[15] that the amount of ethyl iodid retained in the body depended in part on the respiratory rate—the lower the rate, the greater the percentage of retention—it appeared desirable to determine whether the respiratory rate had any influence on the iodin response in the cases treated with ethyl iodid. We, therefore, grouped our cases according to the respiratory rate before treatment was begun. In general, there appeared to be no correlation between the rate of respiration and the lowering of metabolism. The daily fall in metabolism of those patients with respiratory rates of 20 or less per minute was 3.6 points, and of those with rates of 21 or more per minute was 3.8 points.

Conclusion. The daily inhalation of ethyl iodid in doses of 2 to 4 gm. or the daily consumption of 0.2 to 0.4 gm. of potassium iodid

produces as much fall in the metabolic rate of exophthalmic goiter patients as adequate doses of Lugol's solution.

The various characteristics of the response produced by ethyl iodid, potassium iodid and Lugol's solution are similar. The postoperative course following subtotal thyroidectomy for these three groups of patients is essentially the same.

It follows that iodin produces its characteristic changes in exophthalmic goiter independently of the type of iodin compound or the route by which it gets into the body.

It is suggested that potassium iodid solution is preferable to Lugol's solution in the treatment of exophthalmic goiter, being equally effective and less offensive to take.

NOTE.—We are indebted to Miss Helena E. Hardy for invaluable assistance in making these observations.

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HEAD MURMURS.

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I

Not many years after Laennec taught the systematic application of auscultation to the study of disorders of the lung and of the heart, Dr. John D. Fisher[1] read before the Boston Society for Medical Improvement in the summer of 1833 a paper, later published in this journal, in which he expressed the opinion that "auscultation might hereafter prove to be an important means of diagnosis of cerebral as well as thoracic diseases." Almost one hundred years later Harvey Cushing and his collaborator, Percival Bailey[2] write that "cephalic auscultation is a forgotten practice" and furthermore, they say "by a strange human frailty, auscultation of the skull seems to be the one thing most likely to be neglected in a routine neurologic examination." Nevertheless, it should be added that there have been notable exceptions to these more modern statements, for it is said that Sir Victor Horsley made auscultation of the head a routine practice in his examination of cerebral cases; while it is particularly our beloved chief, William Osler,[3] who in 1880 restored Dr. John D. Fisher's "Observations on Cerebral Auscultation" to American medical literature in a brief and characteristic article entitled, "On the Systolic Brain Murmur of Children." The basis of Dr. Osler's paper was the case of a well-nourished, ruddy complexioned child three years of age, who presented a remarkable murmur in the head about which the parents were very anxious. The medical attendant had suggested the possibility of aneurysm but Dr. Osler basing his view on a knowledge of the literature of the time, gave a favorable prognosis. The mother did not appear satisfied and Dr. Osler heard nothing further of the case for some months when he recognized it "in the description of a Case of Supposed Gummy Tumor of the Brain in which the murmur was attributed to the possible existence of a syphilitic growth pressing upon the vessels at the base of the brain." In spite of the two unfavorable opinions dissenting from Dr. Osler's, the child thrived and when seen at the age of seven years was a perfectly healthy girl, the murmur still persisting though sometimes disappearing entirely for a few moments. The bruit had been heard by the mother from the time that the child was a year old and it was sometimes perceived by the girl herself. The murmur was systolic, could be heard

over any part of the head and in the carotid arteries and disappeared on compressing these vessels.

In 1921 Still[4] reviewed the subject of cephalic bruits in children and confirmed the age incidence as reported by other authors. These childhood head murmurs prevail particularly during the second year, occurring in this period two and a half times as frequently as in the first year of life.

Nevertheless, in a routine auscultation of the heads of 7 babies under one year of age, I demonstrated a distinct systolic murmur in 3, all of whom let it be added, were anemic and 1, rachitic.

Anemia and rachitis have been accused as causal agents in the production of the head murmurs of children but while anemia, whether a concomitant of rickets or not, may be a contributory factor, it is certainly not a necessary accompaniment; the bruits have been heard in entirely healthy subjects. There is no record of the persistence of the murmur into adult life. I have heard it as early in life as at two and a half months; and while, as Still points out, it is very infrequent in children over four years, his oldest was fifteen years of age.

The mechanism of the production of the systolic brain murmur of children is not known. It has been assumed that it is due to a "temporary stenosis" of the carotid artery in the carotid canal; that is, the canal does not enlarge as rapidly as the artery increases its volume. On the other hand, it has been suggested that the tortuosity of the carotid at the base of the skull may account for the murmur and that with increasing size of the skull there may be a slight straightening of the artery, making it less subject to sharp turns and kinks, thereby abolishing the bruit. But, whatever the explanation of its causation may be, the fact is that the systolic cephalic murmurs of childhood under discussion are probably without pathologic significance: they are heard in perfectly healthy children although more frequently in those suffering from anemias of various origins.

Recently, I heard throughout the head of a young woman aged twenty-three years, a loud, blowing, systolic murmur which clinically could be associated only with the marked anemia from the effects of which she suffered. For five years she had been the subject of almost continuous hemoglobinuria; the red cells numbered 1,650,000; hemiglobin, 40 per cent.

I venture the opinion that if cephalic auscultation were more frequently practised in the case of highly anemic patients these head murmurs analogous to accidental cardiac and venous bruits would often be discovered.

II

A second group of head murmurs well known to surgeons comprises those accompanying communications between cephalic arteries and

veins. These arteriovenous aneurysms or communications may be intracranial or extracranial. They are acquired in a large proportion of cases by trauma although they and their accompanying head murmurs may be congenital or are classified as "spontaneous."

The simplest example of the acquired intracranial variety is that of a communication between the internal carotid and the cavernous sinus, caused in a large proportion of cases by basal fracture, although it has been reported as occurring in some obscure manner in the course of infections, in pregnancy and as a result of straining efforts. The communication thus established between the internal carotid and cavernous sinus is generally attended by the eventual development of pulsating exophthalmos.[5] But, that pulsating exophthalmos is not a necessary sequel is demonstrated by the history which I shall now briefly relate:

In June, 1911, Mrs. McC., aged twenty-nine years, was thrown to the ground as a result of a carriage accident and was picked up unconscious. The accident occurred directly in front of a physician's office into which she was carried. Blood was flowing from the nose, mouth and ears; a wound over the right brow indicated that her head had been struck on the right side. Regaining consciousness the next day she noticed a noise in her head which she likened to a sound produced by an engine. At times she localized the noise in her ears but usually she perceived it throughout the head. She had difficulty in persuading the doctor to auscultate her skull but when he did so the objective character of the noise was demonstrable. The right eye was "blood-shot;" objects were not distinguished clearly and she thought she was a "little cross-eyed." The ocular signs soon disappeared but it seemed best to consult an ophthalmologist and a neurologist; both, five weeks after the accident, failed to find any ocular abnormality. There was no exophthalmos, no ocular palsy, the vision was unimpaired and the eye grounds, normal. The neurologist, Dr. Byrnes, asked me to auscultate the head and I discovered the bruit characteristic of arteriovenous communication: a loud continuous murmur with systolic intensification heard everywhere over the head from chin to vertex, from face to occiput. It was maximum over the right eye where it had a roaring quality. The murmur was heard also along the tract of the cervical vessels on the right side but not on the left; and it had the same quality as over the right globe. Pressure over the right carotid caused the murmur to disappear but compression of the corresponding artery on the opposite side had no effect. Mrs. McC. disappeared from view for eleven years when Dr. Byrnes reëxamined her and wrote to me that "Since the first visit she has seen Dr. Cushing and Dr. Frazier who both confirmed our diagnosis. According to her statement Dr. Cushing advised against an operative procedure. The noise in her head persists; the murmur is still audible. Perhaps the right eye is a degree more prominent than the left; there is no pulsation."

In a letter dated June 2, 1930, Mrs. McC. writes "worry of any kind makes me worse. By this I mean, the noise becomes loud and rapid." No mention is made of any ocular abnormality.

Thus, there is disclosed the history of a patient presenting the evidence of a communication between the right internal carotid and cavernous sinus with a head murmur persisting for nineteen years without the development of pulsating exophthalmos and escaping surgical interference for nearly two decades.

Incidentally, it may be said that while in the majority of cases pulsating exophthalmos with the concomitant head murmur has had as its anatomic basis communication between cavernous sinus and internal carotid, the ocular condition as well as the head murmur have been noted in aneurysm of the internal carotid, in rare cases of orbital neoplasm and in the still rarer instance of a true aneurysm of the ophthalmic artery.[6]

Another variety of head murmur of intracranial vascular origin is that accompanying the relatively rare cerebral aneurysmal angioma discussed so clearly and attractively by Harvey Cushing and Percival Bailey in their recent monograph on Tumors Arising from the Bloodvessels of the Brain. These aneurysmal angiomas are primarily congenital vascular malformations, and having, from the beginning, both arterial and venous components it is not surprising that the head murmur is described as continuous with systolic intensification.

On the other hand, in some of Cushing and Bailey's cases the murmur is noted as systolic. While the bruit when present together with increased extracranial vascularity may be the decisive element in the diagnosis of cerebral aneurysmal angioma, these authors conclude "that the bruit may be a most variable feature of this vascular condition."

III

Besides the head murmurs of the cerebral aneurysmal angiomas, bruits have been heard in the presence of certain vascular intracranial tumors including meningiomas and gliomas. But, Dr. Charles Bagley and I have heard a cranial bruit in a patient suffering from the effects of a cerebral glioma with a large cyst in the absence of undue vascularity.

A boy, aged fourteen years, had suffered from severe headache with vomiting for fifteen months. During the attacks he frequently complained of a stinging sensation over the right side of the face and tongue. A gradually increasing deafness of the right ear developed. The gait became unsteady, there was some staggering from side to side, chiefly to the left. The boy felt dizzy and frequently had the sensation of falling. There was no nystagmus and diadokokinesia was not disturbed. Both optic disks were choked and there was marked contraction of the left visual field. Finger-to-nose and finger-to-finger tests were well performed. Romberg was positive. Babinski, too, was positive on the right side.

Several weeks before admission while seated beside his sister at dinner he complained of being tired and rested his head on her shoulder. She exclaimed "Oh, Mother, there's a noise in brother's head." When asked about it, the boy for the first time described a roaring in his head. On examination a loud systolic bruit was heard over the entire cranium more marked over the right half, maximum over the right mastoid. Pressure on the right carotid caused the murmur to disappear over the right half of the head while pressure on the left carotid diminished the intensity of the bruit but did not abolish it.

A right subtemporal decompression was performed by Dr. Bagley and "a very tight brain" was exposed. Eleven days later the patient was discharged. The headache had decreased in severity but there was neither subjective nor objective change in the bruit. About three weeks after leaving the hospital the boy's condition was unfavorable. The head murmur occupying a spectacular position in the physical findings, the surgeon in the patient's native town ligated the right carotid artery. It is said that the bruit ceased for a few days but a week later was again plainly heard. The patient was once more received in the hospital about two months after his first admission and a left subtemporal decompression was performed. Death occurred ten days later.

The autopsy, performed immediately after death and without preliminary fixation of the brain, revealed a very marked displacement downward of the hind brain into the foramen magnum with angulation of the vertebral arteries which had been dragged downward into the vertebral column to a point sufficient to produce angulation of these vessels. This herniation was found to be due to the very high position of the neoplasm, which was located chiefly in the midline. The usual dilatation of the ventricles was present.[7]

In this case the cephalic murmur was a confusing sign and the autopsy revealed the only probable explanation in the angulation of the vertebral arteries. Previous to the postmortem examination the absence of extracranial vascularity and of epileptiform attacks rendered the diagnosis of aneurysmal angioma hazardous. To assume that in addition to a cerebellar growth there might be a true aneurysm of a cerebral artery to account for the murmur was equally venturesome since we were well aware of the extreme rarity of a bruit in the presence of an actual sacculated intracranial aneurysm.

The rarity of the opportunity to hear a murmur in the case of a true aneurysm situated within the skull was revealed by Beadles in 1907. In a critical review of the subject of aneurysms of the larger cerebral arteries Beadles,[8] while commenting on the erroneous statements in textbooks along this line, disclosed the rather startling fact that in a study of 555 proved cases of true intracranial aneurysms (not arteriovenous aneurysms) there were only 2 in which a murmur had been heard during life. These were demonstrated postmortem as uncomplicated intracranial aneurysms of the vertebral and internal carotid arteries respectively.

Beadles ventures to express the doubt, "if more than a couple of living physicians or surgeons have seen a case in which a murmur has been audible, and in which the evidence is conclusive that the patient had a true aneurysm of a cerebral artery." In the monograph to which reference has been made Harvey Cushing and Percival Bailey have asserted that "in the hospital series of true intracranial aneurysms a bruit has been observed in only a single instance" and that was not heard until after the operation had been performed.

Through the courtesy of Dr. Bagley I had the rare opportunity of hearing a systolic cephalic murmur in the case of a patient, the

subject of an aneurysm of an anterior cerebral artery. The details have been published by Dr. Bagley[9] and in abstract are as follows:

A girl, aged twelve years, was suddenly seized with severe headache and vomiting about a month before hospital admission. Lumbar puncture revealed a bloody cerebrospinal fluid. Marked improvement followed, although she was rather dull and vision was blurred. A month after the first attack of headache she had a second severe attack with convulsive seizure, diplopia and blurred vision. She was then brought to Baltimore and admitted to the Church Home and Infirmary. The girl was stuporous, though she could be aroused. There was a high degree of choked disk with retinal hemorrhages; the right pupil was larger than the left. A loud systolic murmur was audible over the entire head, maximum over the temporal regions. On inquiry, the child said that she had heard the murmur for a long time. A lumbar puncture again yielded bloody cerebrospinal fluid. To relieve pressure a right subtemporal decompression was performed. Death ensued four days later. At autopsy, there was disclosed a large hemorrhage between the hemispheres, extending from the base into the left lateral ventricle. Part of this area showed an organized bloodclot, the result of bleeding which evidently caused the first severe headache. An aneurysmal dilatation of the right anterior cerebral artery was found, the rupture of which accounted for the large amount of fresh hemorrhage which was also present.

In the same publication in which the foregoing case is reported Bagley mentions a cephalic murmur dependent on a congenital vascular anomaly involving the venous structure of the dura. The greatly dilated venous sinuses and their tributaries lay in deep depressions channeled in the skull. During the life of the subject, a woman aged twenty, a heart murmur with cardiac enlargement had been found at twelve; a head murmur at sixteen. The venous plexus disclosed at autopsy involved chiefly the occipital and cerebellar veins. The nosologic status of the anomaly was not determined.

IV

In introducing the subject of cephalic murmurs arising from arteriovenous communications of cranial vessels it was stated that these communications might be intracranial or extracranial. The discussion of murmurs originating from intracranial arteriovenous communications led us into bypaths from which we now return to consider the head murmurs resulting from vascular communications which are chiefly extracranial although in one group the vessels of the diploë are concurrently involved. These are either obviously congenital or follow trauma.

Miss Ruth K's head murmur is plainly due to a congenital aneurysmatic condition, leading to a striking malformation of the left external ear. Ever since she can remember the left ear has been larger than the right but at puberty the malformation became accentuated. At this time she discovered that when the auditory canal was closed by placing the tip of her finger in the external meatus she was conscious of a noise in her head. In November, 1929, when Miss K. was twenty-six years of age, her left ear was about

half again the size of the right, its surface irregular and lobulated, the lobulations were evidently due to huge varices. The color of the ear was variegated, flesh tints alternating irregularly with purple and red. The ear moved upward and backward with each pulse beat. In front of the pinna dilated, pulsating vessels extending almost to the external canthus of the left eye were visible. A small exostosis was palpable beneath the chin a little to the left of the median line. The patient attributed this outgrowth to striking her chin in 1918. Just in front of the exostosis there was a pulsating mass of vessels consisting apparently of veins, the mass measuring about 1 cm. in diameter. On palpating the ear a thrill was detected and corresponding with the thrill a loud continuous murmur with systolic intensification could be heard. The murmur was at its maximum over the posterior aspect of the ear but was audible throughout the left half of the face. It could also be heard but less distinctly over the right half of the mandible. Pressure on the left carotid diminished the intensity of the murmur but when in addition the right carotid was compressed the bruit disappeared.[10]

On two occasions, the last on June 6, 1930, Dr. Bagley dissected and excised masses of varices in the hope of eventually discovering and obliterating an arteriovenous fistula between trunk line vessels. The ear has diminished in size and the bruit, while still present, has lessened in intensity.

Another example of a head murmur, which probably has a congenital basis in the persistence of communications of the primary vascular "anlage" resulting in later life in the formation of anastomotic channels,[11] is afforded by one of Dr. Barker's patients.

Mrs. McW., aged fifty-nine years, had complained of a noise in her left ear of seven months' duration. The noise appeared suddenly without apparent cause, was intermittent at the onset and was likened to the puffing of an engine. Subsequently, it became constant and sounded to the patient like the chirping of a bird. She discovered that the sound was synchronous with the heart beat, was more intense when in the recumbent posture, thus disturbing her sleep, and was accentuated by stopping the left auditory meatus with the finger tip. It was also learned that several people had heard the noise with the naked ear, that the patient could eliminate the sound by temporarily holding her breath and by pressing on the left mastoid region.

Over this area a diffuse pulsation was detected but no mass could be palpated. With the stethoscope just above the left mastoid process a loud, musical, systolic murmur was audible. The bruit could be heard in diminishing intensity downward into the suboccipital region right to the median line. Light pressure over the left carotid artery obliterated the bruit, and the same result could be obtained by pressure above and below the point of maximum intensity. Indeed, the murmur could be made to disappear by pressure at so many points in the affected area that no single vessel could be held responsible for the murmur. Dr. Dandy ventured the opinion that the condition was aneurysmatic and involved occipital arteries and veins with extension into the diplöe.

An eventual surgical interference was suggested but the patient withdrew from observation and the ultimate outcome is not known.

A case almost identical with the one just described was reported by Küttner[12] and was attributed to the formation of an angioma arteriole racemosum with the occipital artery running an abnormal

course. A man, aged forty-eight years, suffered for three years from a constantly increasing noise in the ear, synchronous with the pulse. Pulsation in the region of the occipital artery was present; a bruit was audible. At the operation the affected area was found copiously permeated with arterial vessels. The occipital artery and its mastoid ramus ran abnormally through a long bony canal. The canal was opened throughout its whole extent. However, the vessel could not be isolated but had to be removed by means of the raspatorium. The resultant bleeding from the bone was controlled by sterile wax with which the whole canal was filled. The murmur disappeared and was still absent at the time of the report four months later.

A head murmur dependent on superficial arteriovenous communication of traumatic origin is illustrated by the following case:

A young man, aged twenty-seven years, was struck on the right temple by a baseball, was stunned, and fell to the ground. After a few minutes he arose and completed the game. A week later he was conscious of a noise in his head. He had difficulty in inducing his physician to listen to his head. Eventually, the diagnosis of arteriovenous aneurysm involving the superficial temporal vessels having been made, a surgeon in the South ligated the temporal artery. He was relieved of the noise for two days, when it returned; but after operation it was audible to himself only when he lay on the right side or closed the right auditory canal, as for instance by placing a telephone receiver to the ear on the affected side. A year after the accident there was a small pulsating mass just in front of the right tragus. On auscultating this area a loud continuous blowing murmur with systolic intensification was audible. At times it had a slightly musical quality, was sharply localized to the area of the stethoscope bell, and could be made to disappear by pressure on the temporal artery below the swelling. Dr. Bernheim removed a section of the artery, and a mass of dilated tortuous veins, some of which were included in a piece of excised temporal muscle. The patient awakened from the anesthetic, the noise had disappeared and the cephalic murmur was, of course, absent.

Considering the rarity of proved arteriovenous aneurysms between trunk vessels as the result of contusion, it is probable that the basis of the head murmur in this case of baseball injury was established by communications between smaller vessels in the vascular temporal area.

V

Another group of cephalic murmurs is devoid of surgical interest. It includes subjective and objective sounds which are transmitted headward in the direction of the blood current from their origin in atheromatous and possibly dilated carotid arteries. Other evidences of marked arteriosclerosis are present.

Mrs. D., aged seventy-five years, Dr. Barker's patient, complained of noises in the head, constant headache and dizziness of several years' duration. In addition she suffered from the angina pectoris of effort. She com-

pared the head noise with the ringing of bells. In front of either ear a faint short musical systolic bruit was audible. The same murmur was heard beneath the angle of the jaw corresponding with the carotid artery on the left side.

Similarly, Mrs. S. complained in her sixty-eighth year of a noise in her head which she likened to the thumping of an engine. When she was asked to imitate it she produced a replica of the cephalic murmur which I thereupon heard.

Just above the left clavicle over the inner half of the fossa there was a systolic bruit which became more intense as one passed up along the line of the carotid. It could be heard distinctly behind the left ear, in front of it, and indeed, in the left temporal region. It was maximum about the middle of the sternocleidomastoid. Over the middle of the sternocleidomastoid, on the other side, an extremely faint musical murmur could be detected. Later in the year Mrs. S. began to complain of substernal pressure on exertion, and on one occasion suffered a major attack of angina pectoris. One morning three years later she arose as usual, but coming down-stairs she complained of a pressure in the sternal region radiating to her back between the shoulder blades. At night between nine and half past nine she ascended the stairs, was about to retire when she said she was going to faint. With these words she fell, "crumpled up," as her daughter described it, and was dead.

Like these murmurs presumably dependent on atheromatous carotid arteries and conducted to the skull, there are a few other bruits originating below the level of the head which can be heard by cranial auscultation.

Of interest are the occasional cephalic murmurs heard in certain patients suffering from exophthalmic goiter. Considerable discussion arose as to their nature after Snellen[13] first described one which he heard when auscultating the eyes of a patient afflicted with Basedow's disease. Snellen interpreted the murmur as vascular in origin and compared it with the placental bruit. However, in his encyclopedic volume "Die Basedow'sche Krankheit," Sattler[14] devotes several pages to a critical evaluation of Snellen's orbital murmur, and the conclusion is reached that it is not of vascular source but is a muscular sound due to contraction of the orbicularis. Nevertheless, there is no question that subjective and objective head murmurs of vascular origin are present in a few patients afflicted with exophthalmic goiter. The similarity of the muscular sound of the contracting orbicularis to a rumbling vascular murmur is easily demonstrable to anyone who will ausculate the closed eyelids even of a normal subject.

Taking care to exclude this error by proper auscultatory technique, I heard, throughout the head of a lady aged sixty years, suffering from exophthalmic goiter, a short blowing systolic murmur. The bruit was maximum over the closed eyes. It was not heard by the patient. A similar murmur was present over the struma. Dr. Follis performed a subtotal thyroidectomy and the cephalic murmur disappeared. The impression gained was that the murmur was transmitted to the head from its point of origin in the enlarged and probably tortuous vessels of the goiter.

The murmur of a cardiac valvular lesion may also be conducted to the head. In the following instance the conduction was probably through the framework of the body.

A boy, aged six years, acquired mitral insufficiency as the result of a rheumatic infection. Cardiac dullness was increased, a loud blowing systolic murmur was heard all over the precordium, maximum over the mitral area, loudly transmitted to the back. A systolic murmur was audible all over the head. While it was well heard over the vertex it was louder over the chin and lower occipital region. The murmur was likewise transmitted to the shoulders and down the upper two-thirds of the arms. It was not heard by the boy. Before his death two years later he developed aortic insufficiency, which in no way altered the cephalic bruit.

VI

Finally, we come to consider two examples of head murmurs arising in presumably healthy individuals without apparently adequate causes, lasting in one case about six weeks, in the other, about six months and disappearing without untoward results to either.

The first patient is a physician, long associated in several capacities with the Johns Hopkins University and Hospital. He was in his forty-eighth year, when, ten years ago, the following episode occurred. He called me by telephone to tell me that for two days he had noticed, at intervals, a peculiar throbbing sound in the right half of his head. First he mistook the sound for the noise of a pump connected with the water-supply service but he was soon convinced that it originated in his head. Toward the end of the second day the sound assumed the character of a murmur synchronous with the heart beat. It was so loud that he ventured to ask his wife to place her ear against his head and in this way she heard distinctly a "whiffing" sound just behind the right ear. The doctor attempted to transmit the head murmur to me by telephone. The story would have been more dramatic if I had heard it but I failed to distinguish it through the receiver. However, the following morning I called on him, and was told that for three weeks he had had a rather severe cough which he attributed to a tracheitis. During the latter two weeks of the cold, he had a headache chiefly on the right side, generally passing off after breakfast. Then came the noise in his head to which I have referred. The examination revealed no evidence of peripheral arteriosclerosis; cardiac dullness was not increased and the heart sounds were clear. There were no murmurs over the carotid at the root of the neck. Over the right angle of the jaw a distinct blowing systolic murmur was heard and while the bruit was audible all over the head it was much more marked over the right half and maximum over the right mastoid region. Here it had a whistling, singing quality and continued well into diastole. Pressure on the right carotid obliterated the murmur. When the patient swallowed, and maintained the position of deglutition, the murmur also ceased. There was no exophthalmos; the eye grounds were normal. Subjectively, the murmur increased during the following three weeks, was accentuated by exertion and then was appreciated by the patient through the left half of the head. The bruit seemed to him loud, and usually systolic, but frequently appeared to run into diastole. About six weeks after the onset the murmur was intermittent and finally disappeared completely.

Today, ten years later, there is nothing in the doctor's condition which could be attributed to the vascular accident which must have been the basis of the cephalic murmur.

While the doctor's cephalic murmur was under observation a similar case came to my notice.

Mrs. B., aged forty-seven years, was seen in January, 1920. In August, 1919, while swimming she was overwhelmed by a wave, and immediately thereafter experienced pain in the left half of her face. Simultaneously she became aware of a pounding noise in the left ear which she likened to the exhaust of an engine, a sound which seemed to emanate from without. The eyes at first felt bulging but this sensation soon disappeared. During the following month she consulted Dr. Bordley, the aurist, who found the ears normal. The head noise persisting, the patient consulted Dr. Thayer, who in turn referred her to me because of my interest in cephalic murmurs. The peripheral arteries were not thickened, cardiac dullness was not enlarged, the heart sounds were clear. There was no murmur over either carotid but as one passed up the left side of the neck a continuous machinery murmur, with systolic intensification, was audible when a point opposite the angle of the jaw was reached. Indeed, the murmur was heard all over the head but louder over the left half. Its maximum intensity was over the left mastoid, where the bruit had a higher pitched and almost whistling character. Pressure on the left common carotid instantly stopped the murmur. The patient cried out: "Why that stops it—the first time since August."

In a letter dated February 27, 1920, six months after the swimming episode, the patient wrote that "the pulse beat that has been present with me constantly left me on Saturday, February 21." On arising from bed that day the patient was nauseated for a short while. The nausea having subsided she had her breakfast. Later in the morning she took a walk, and discovered that the head noise had disappeared but in its place she had acquired a severe pain in, over and under the left eye and in back of the left ear. The pain disappeared in the course of a few days and at the time of writing she described herself as perfectly well.

The mechanisms by which these two cephalic murmurs were brought into being, and by which their spontaneous disappearance was accomplished, can only be surmised. Each murmur, particularly that in the case of the lady, possessed the character of an arteriovenous bruit. It is, therefore, proper to assume a communication between the internal carotid and the cavernous sinus since this communication is the most common intracranial lesion productive of a continuous murmur with systolic crescendo. Yet, trauma causing fracture of the base of the skull is usually the antecedent factor in the production of this communication, followed as a rule by pulsating exophthalmos. In the two cases under consideration exophthalmos did not supervene, neither did a violent trauma precede the production of the murmur. However, the evolution of these intracranial arteriovenous aneurysm is not uniform, since one of our patients thus afflicted, and in whose head the murmur has persisted nearly twenty years, has no exophthalmos. Violent trauma is not a necessary antecedent as recorded cases of so-called

"idiopathic" pulsating exophthalmos show. In one of these "spontaneous" cases of intracranial arteriovenous aneurysm, coughing was apparently the exciting cause.

Could not coughing be assumed to play a similar rôle in the doctor's case just reviewed? So, too, in the second case under consideration, might not the impact of the wave or the straining incidental to freeing the respiratory tract of the sea water induce the junction of internal carotid and cavernous sinus and the consequent murmur? An affirmative answer is justified by the reports of the cases which are said to follow not only coughing but vomiting, straining at stool, the effort of washing windows and injuries to the skull so slight as to make the existence of a basal fracture unlikely.[15]

In attempting to explain the disappearance of these arteriovenous murmurs and the underlying intracranial vascular lesion, it should be said that spontaneous cures of even the end product of communication between the internal carotid and cavernous sinus, namely, pulsating exophthalmos have been described.

In the well-known traumatic case reported by Oliver,[16] Dr. Frazier ligated the right common carotid and the left internal carotid with some reduction in the intensity of the symptoms. Twenty-one months after the second ligation the patient collided with a playmate. That day there was a marked diminution in the bruit and exophthalmos, and on the following day the murmur disappeared and never returned.

At a meeting of the Societé de Chirurgie de Paris in 1909, on the occasion of a discussion on aneurysm of the internal carotid and cavernous sinus, Périer[17] narrated briefly a history illustrating the spontaneous healing of this arteriovenous aneurysm. A young girl was thrown from a swing. She was cast violently to the ground striking the back of her head and losing consciousness. The following day a loud cephalic murmur was audible. Without active interference, the murmur gradually diminished, disappearing entirely at the end of several weeks.

Hence, the assumption that spontaneous healing of an arteriovenous fistula with disappearance of the cephalic murmur occurred in each of our 2 patients under discussion finds corroboration in the literature pertaining to the subject.

Summary. Some examples of cephalic murmurs are here presented which originate from either intracranial, extracranial or infracranial sources.

In the intracranial group the systolic "brain murmurs" of childhood were discussed. The contributing factor that anemia sometimes plays in their production was mentioned, and evidence was adduced to show that accidental cephalic murmurs might be found more frequently in adults, if auscultation of the skull were more often practised.

The bruit of arteriovenous aneurysm of the internal carotid and cavernous sinus was repeatedly reviewed, largely because of 2 patients in the series in whom head noises with corresponding murmurs appeared without apparently adequate causes only to disappear in even a more obscure manner. Arguments were advanced to establish the probability that each of these two murmurs had as its anatomic basis an arteriovenous fistula which underwent spontaneous closure with consequent disappearance of noise and bruit.

Reference was made to the head murmurs dependent on intracranial vascular tumors. A murmur resulting from angulation of the vertebral arteries, caused by foraminal herniation of the cerebellum as a consequence of the presence of a cerebellar cyst, was described. The rare murmur of an actual aneurysm of a cerebral artery was illustrated by a case.

Murmurs of extracranial origin were exemplified by instances of congenital arteriovenous aneurysms and by one of traumatic origin.

Those head murmurs having an infracranial origin were demonstrated by descriptions of bruits propagated from atheromatous carotid arteries, from the struma of Basedow's disease and from a cardiac vascular lesion.

Finally, it should be added that the chief object of this paper is to revive interest in cephalic auscultation—a well-nigh lost art!

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OBESITY, CONSTITUTIONAL OR ENDOCRINE?

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The question of obesity has occupied the minds and pens of so many workers that it seems scarcely necessary to add another publication. Endocrinologists, especially, have taken a great interest in the subject, and as a result we find the literature filled with references to the relation between endocrine disorders and obesity. While we grant that endocrine dysfunction *may* be a cause of obesity we feel that these cases form a small, numerically almost insignificant part of the obese patients that present themselves in the clinic. It shall be the purpose of this report to review briefly the present concepts of the nature of obesity and to present a case that illustrates the dangers of an "endocrine diagnosis" in cases which, on careful study, reveal another, more likely, basis for the obesity.

One of us (J. B.) has for many years emphasized the importance of the constitutional nature of obesity. However, the exact limitations of this concept have not been understood, and in the minds of many "constitution" is a scrap heap into which are thrown all speculative medical concepts. We wish to stress the significance of an understanding of "constitution" as an aid in the interpretation, not only of obesity, but of disease processes in general.

For a long time the question of the exogenous or endogenous nature of obesity has been discussed. In a very recent publication Newburgh[1] reopens the problem and doubts the existence of endogenous obesity. It is interesting to contrast this opinion with that of Gigon,[2] who denies the existence of an *exogenous* obesity.

While we have great respect for the thorough and careful studies of Newburgh, we do not believe that he has added to the clarification of the problem. True, he has shown that in obese patients the energy expenditure is less than the caloric intake and that the patients are on a positive energy balance. He has also shown definitely that if the energy intake be reduced below the output these patients lose weight. However, he has not explained why it is that these obese patients consume more food than they need to maintain normal weight or why their energy expenditure on a given caloric intake is less than that of normal people.

The concept of the endogenous nature of ordinary obesity does not deny the principle of the conservation of energy, as some of its opponents seem to believe. It accepts as obvious the fact that obesity is due to an intake of food that exceeds the energy output. However, it goes further and attempts to explain the mechanism of this disturbance.

Obesity must be considered as a failure of the mechanism that normally keeps the weight of adults constant. It is quite remarkable that this mechanism is so perfect in the normal adult that he goes on from year to year always altering either his energy expenditure or his food intake, and yet the regulatory processes proceed at the same rate so that his weight remains constant. If the food intake be voluntarily increased then an increased output of energy occurs, or if on the other hand, changes in activity take place, then corresponding changes in appetite occur. As a result the normal person, paying no attention to either the extent of his activity or the intake of food, arrives at a perfect balance between the two.

Under the term exogenous obesity have been considered those cases thought to be due obviously to gross variations either in the food intake or energy output. Attention was called to brewers, inn-keepers, bakers and butchers, as examples of people who became fat because of great caloric intake. Another group was signaled out as being fat because they were indolent and did not carry out sufficient muscular exertion. Yet, if one studies a large series of obese patients one is struck by the fact that occupation plays an insignificant rôle. In Bauer's[3] series of more than 400 cases he could not establish any relationship between obesity and those occupations that are reputed to allow opportunities for overfeeding. Similarly, restricted activity alone cannot explain the usual genesis of obesity. Normal people decrease their energy intake when their activity is reduced and automatically make adjustments that prevent the laying on of fat. The anorexia that follows confinement to bed is too well known to require emphasis. In a corresponding manner increased feeding is compensated for by increased cellular activity.

What then, is the mechanism that allows obese patients to remain for a long period of time in a positive energy balance? Why do they continuously exceed their caloric necessity? The understanding of the problem of obesity requires an answer to these questions rather than experiments to prove the obvious fact that obese patients eat more than they expend—their being obese is proof of that. We must, then, center our attention upon perversions of the normal relationship between appetite and energy expenditure. When the regulation is perfect the individual is in equilibrium and there can be no question of obesity. It is only when the mechanism fails and the appetite exceeds the energy requirements that obesity appears.

To result in obesity this regulatory mechanism may be affected at two points. Either the appetite may increase or the energy expenditure may decrease, without the proper regulation of the opposing function.

That perversions of appetite occur in organic and functional disease of the central nervous system is well known. "Cerebral obesity" is a rare but distinct type of overweight, and can be seen in encephalitis and other lesions affecting the midbrain. However, there is no evidence to prove that the increased appetite is not the result of a tendency to obesity occasioned by the lesion rather than that the appetite disturbance is primary. The distinction whether a nervous lesion causes a primary polyphagia or whether the polyphagia is merely the sequel of a newly instituted tendency to obesity cannot be settled easily. The relationship between growth (or obesity) and appetite is well shown in the experimental work of Putnam, Benedict and Teel.[4] In their studies in the experimental production of acromegaly in dogs by the injection of hypophyseal extracts, they noted rapid growth and enormous increase in appetite. One would scarcely say that the anterior lobe of the pituitary gland stimulates the appetite in the sense that bitters do. One would not say that these dogs grew because they ate more. They ate more as an inescapable result of a newly instituted tendency to growth which is a specific action of the anterior pituitary lobe. The dogs did not grow *because* they ate more, but they ate more because they were growing. The increase in appetite is a result, not a cause.

In this connection we wish to point out that increased appetite alone does not necessarily result in obesity. In the cases[5] of hyperinsulinemia with hypoglycemia and extreme hunger periods, obesity was not noted although the patients were fed large amounts of carbohydrate to combat the hypoglycemia. This does not lend support to the suggestion of Falta that obesity has as its basis an increased appetite conditioned by hyperactivity of the insular apparatus.

We have indicated that an increase in appetite need not necessarily lead to obesity. Similarly, it is true that depression of the oxidative changes is not always accompanied by an increase in weight. Although on the one hand we have myxedema, castration and convalescence as examples of conditions in which a lowered basal metabolic rate is often accompanied by a tendency to obesity, on the other hand we have hypophyseal cachexia, Addison's disease and pluriglandular insufficiency where, in spite of profound depressions of the basal metabolic rate, the patients become cachectic rather than obese. In this connection it is interesting to recall Bauer's[6] notation that Heinbecker found among Eskimos a distinct increase in the basal metabolic rate, although these people are characteristically obese. Similarly, Sokhey[7] found among East Indians, who are usually thin, a lower basal metabolic rate than is normal for Europeans.

Kestner[8] and the Hamburg school have emphasized the importance of the specific dynamic action of the foodstuffs in the etiology of obesity. They feel that a decrease in the specific dynamic action may account for cases of obesity. It is only necessary to point out that in those conditions in which there is an almost complete abolition of the specific dynamic action, as in Simmonds' disease, cachexia, rather than obesity, is the rule. Then, too, these changes noted by Kestner in obesity may well be the result of the obesity rather than its cause. It is obvious that if there exists a tendency to deposit foodstuffs rather than to burn them the oxygen consumption and the specific dynamic action will be decreased.

It is self-evident that a decrease in the amount of muscular exertion or a more economical exhibition of the usual muscular exertion would lead to obesity if all the other factors remained constant. We have indicated that normally these "other factors" do not remain constant, but a readjustment on the new level occurs and the intake is again only sufficient, not excessive. Inactivity or muscular exertion alone do not determine obesity or thinness. If this were true, all sedentary workers would be fat and all laborers thin. However, the clerk who is "nothing but skin and bones" is too well known to make it necessary to insist upon the lack of corellation between physical exertion and obesity.

The "balance" theory of obesity assumes a *primary* increase in appetite or a *primary* decrease in energy expenditure. We have indicated that an increase in appetite *need* not result in obesity, and that a primary reduction of metabolism, whether by depression of the basal metabolic rate, decreased specific dynamic action of the foodstuffs or a lessened amount of energy expended in muscular work need not necessarily, or even usually, lead to obesity.

If we are to abandon the "balance" concept of the nature of obesity what have we to offer in its stead? When we recall that Bauer could demonstrate the familial incidence of obesity in some 88 per cent of his cases, and that von Noorden found 70 per cent of his obese patients to come from families in which obesity prevailed, may we not regard these findings as significant in the origin of the obesity? Eating from a common table or following a common table tradition alone cannot explain these figures. These people become obese even if they eat exclusively outside their homes. It is a common observation (Bauer) that the most severe grades of obesity and emaciation can be seen in the same family among people who live from a common table. Apparently, there may be a defect in the congenital factor that determines and regulates weight, and this defect may manifest itself in the exhibition of obesity or its direct opposite.

Even the most ardent supporters of the balance theory cannot deny the fact that when fat accumulates it usually localizes in definite, fixed regions. The obese female of the "typus Rubens"

with fat hips, large breasts, obese lower abdomen and fat thighs is too well known to make it necessary to insist upon the tendency to specific localization of fat in women. In men, during the period of sexual activity, fat deposits in these regions are inhibited, and they deposit fat at the back of the neck, upper abdomen and arms. However, before maturity as well as after castration and the loss of sexual function, men acquire the female distribution of fat, probably as a result of the loss of the inhibition that the male sex hormone has on the location of fat deposits.

That there is an independent, local, predestined tissue disposition to obesity is proved by those cases[9] recorded where an autogenous tissue transplant from the abdominal wall to the back of the hand had been made. It is known that the back of the hand rarely becomes fat, yet in these cases a distinct, local, unilateral obesity occurred at the site of the transplant. This indicates that the transplanted abdominal wall, separated from its previous nerve and blood supply, retained its *lipophilia*, that is, its irresistible tendency to accumulate fat.

The constitutional concept of obesity considers this exaggerated tendency of some tissues to store fat, and possibly water and salts, as the *primary* factor in the causation of the obese state. It regards this tendency as congenital and hereditary, although, like many other congenital factors, it may not become evident for many years after birth.

If we locate the genesis of obesity in a constitutional destiny of the tissues of certain people to store fat then we can understand a disturbed balance between energy intake and expenditure as a necessary sequel of this almost irresistible tendency. We can also understand those cases of obesity, common in the experience of everyone, where in spite of rigorous diet and exercise, we are unable to reduce the fat from the areas where it is most obvious. We know of patients who suffer from a severe grade of inanition and even emaciation without any effect on the fat deposits that we would most like to influence.

The concept of constitutional obesity regards the lipophilia of the tissues as the basis and cause of the metabolic disturbance. It does not deny that obese patients are on a positive energy balance. It explains this perversion of metabolism as the result of a congenital factor, already present in the fertilized ovum, that destines the organism to accumulate fat. Obesity is not the result of overeating, but overeating may be an inescapable consequence of an inborn tendency to obesity.

Von Bergmann[10] has very aptly compared the factors resulting in growth with those resulting in obesity. Just as a youth grows, although his activities make great demands on his caloric intake, so some tissues accumulate fat, often at the expense of the needs of other organs. In this connection, Zondek,[11] Striek,[12] Lowen-

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stein[13] and Bauer[6] have observed cases with increased basal metabolic rate, manifestations of inanition and emaciation of parts of the body in which there existed a high grade of localized obesity. Such findings are not readily explained by a theory of obesity that begins and ends with a disturbance between food intake and energy output.

Case Report. The patient, a housekeeper, aged forty-seven years, has suffered from progressive obesity since a thyroidectomy, which she underwent in 1923.

The patient's mother died of pulmonary tuberculosis. Seven siblings died as children. Father is alive and well.

The patient was quite well until the outbreak of the World War. The unrest caused by the hostilities and the death of a brother at the Front occasioned the patient great uneasiness. It was later noted that her eyes had become prominent and that a goiter had appeared. She began to suffer from palpitation and involuntary twitchings. She sought the clinic of Professor Mannaberg, where the diagnosis of hyperthyroidism was made. At this time the patient was of normal stature and weighed 50 kg.

Photograph of patient.

At that time, 1921, Mannaberg was investigating the effect of radiation of the ovaries on the progress of Graves' disease. The patient was radiated and became amenorrhoic, but the course of the Graves' disease was uninfluenced.

In 1923 a partial thyroidectomy was performed in the clinic of von Eiselsberg. The course of the patient was uneventful, and she was discharged from the clinic in September, weighing 49 kg.

Since 1923 the patient has been growing progressively more obese, and now weighs over 100 kg., an increase of more than 100 per cent of her former weight.

The amenorrhea that followed the Roentgen treatment was complete for one year. After this the menses returned, at first irregularly, but later they became quite normal under ovarian therapy.

Physical examination reveals a considerable obesity, the distribution of which can be seen in illustration. There is a residual exophthalmos and some enlargement of the parotid glands, as is not uncommon in obesity. The pulse rate averages 90 per minute. Blood pressure readings have varied between 170 systolic and 95 diastolic and 130 systolic and 80 diastolic. The hemoglobin is 94 per cent and the red cell count 5,124,000; white blood cells, 7300; polymorphonuclear, 59 per cent; lymphocytes, 33 per cent; monocytes, 4 per cent; eosinophils, 1 per cent; mast cells, 3 per cent; blood sugar, 120 mg. per cent; Roentgen ray of the sella turcica normal; basal metabolic rate is −3. The general physical examination reveals nothing else of significance.

Discussion. A careful analysis of the cause of the obesity in this case reveals the dangers encountered in studying obesity accompanied by disorders in endocrine function.

The endocrine system certainly exerts an important influence on the total metabolism. One has only to recall the obesity that usually follows castration, the obesity of Froelich's syndrome or of adrenal origin to be convinced that endocrine factors can disturb the relation between energy intake and expenditure. That this balance can be shifted in the opposite direction by endocrine dysfunction is illustrated by the cachexias encountered in Graves' disease, pluriglandular sclerosis and F. Simmonds' disease.

It is one thing to be aware that endocrine disorders *may* cause obesity and quite another to believe that the usual cause of obesity is to be found in the endocrine organs. Bauer[6] found that only 2.6 per cent of 275 cases of obesity had their origin in clinically detectable disturbances of the glands of internal secretion.

In the cases cited above it is the obvious tendency to associate the obesity with either the thyroid or the ovaries, as each of these glands has shown a distinct abnormality. However, an analysis of the clinical picture shows that no causal relationship can be established between either of these glands and the obesity. That we are not dealing with a postoperative hypothyroidism is shown by the absence of any of the signs of this condition. The skin is normal, moist and warm and the patient perspires freely. The pulse rate is 90 per minute and the temperature and the basal metabolic rate are normal. When thyroid extract was administered the patient showed toxic symptoms without any appreciable effect on her weight. There is, then, no evidence to make one believe that the obesity is thyrogenous. A thyroidectomy is not necessarily the cause of an obesity that follows it. It may merely be the releasing moment that allows a congenital tendency to become manifest.

Similarly, we can find no firm basis upon which a diagnosis of hypogonadal obesity can be established. The amenorrhea that resulted from the Roentgen treatment began in 1921, and it was not until 1923 that the patient became obese, and now that the ovarian function is reëstablished, as manifested by the return of menstruation, the patient's obesity continues unchecked. In addition, the genitalia show no evidence of abnormality clinically, so there is no evidence upon which a diagnosis of hypogonadal obesity can be based.

We can find no evidence to support the view that the obesity may be of hypophyseal origin. We do not believe that a "hypophyseal distribution" of fat exists. There is, also, great doubt whether pituitary disease without involvement of the midbrain centers can lead to obesity at all. Too often one sees cases called hypophyseal obesity because they cannot be shown to be either hypogonadal or thyrogenous, and the author feels that some endocrinologic basis for the obesity must be found. The more carefully obese patients are studied, the rarer will be "pituitary obesity." The case presented shows no abnormal pituitary function; the growth, hair distribution, libido and genitals are normal and there are no evidence of a pituitary tumor.

As in so many other cases of obesity, the key to the understanding of this case lay in a study of the family and an appreciation of the constitutional, familial nature of the affection. A sister of the patient weighs 83 kg., although rather short. This sister has a daughter who weighs 80 kg. at seventeen years of age. This occurrence of obesity in sister and niece is certainly more than coincidence. It occurs too often to be explained on that basis as the statistics of Bauer and von Noorden show. The sister has no thyroid or ovarian disturbance, eats at a different table and yet develops an obesity of the same character and distribution as the patient who has had so many endocrine disorders. The thing they have in common is not an inherited excessive appetite, but a constitutional tendency to obesity which is also manifest in the succeeding generation.

Summary. 1. In this very brief report we have attempted to outline the insufficiencies of the "balance" theory of obesity and to indicate the importance of an understanding of the significance of the peripheral tissues in the usual genesis of obesity.

2. We have indicated the congenital and hereditary nature of the obese state and wish to stress its etiologic importance.

3. Endocrine obesity exists, to be sure, but obesity resulting from demonstrable endocrine dysfunction is uncommon (some 3 per cent of the cases studied).

4. We wish to insist that, although there may be other causes for obesity, the *usual* one is to be found in the constitutional makeup of the individual and not in exogenous factors.

5. A case is reported which could easily be taken for an endocrine

obesity, as it had developed after a successful operation for exophthalmic goiter. In reality it represents a case of constitutional inheritable obesity.

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THE METABOLISM OF GALACTOSE.

IX. The Influence of Hepatic Dysfunction on Tolerance.*

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In a series of previous papers[1] the writer and his associates have discussed the normal human tolerance for galactose and a variety of factors exercising influence on its level. The present paper deals with influence of hepatic dysfunction as determined by objective methods on the power of the organism to utilize this sugar. The use of galactose for function testing was first suggested by Bauer[2] in 1906 as a means of evaluating the level of hepatic activity, but the failure of the subsequent observers to recognize intrinsic sex and age differences and the lack of uniformity in the criteria adopted led to seemingly contradictory results and gradually caused its discontinuance as a test substance. Its use has been revived by the senior author, after a careful and extensive study of the conditions limiting its application, and today it forms the basis of a quantitative vital function test of wide applicability and differential significance.

* Presented before the Biochemical Section, American Chemical Society, Atlanta, Ga., April, 1930.

Further, in the last few years methods for the estimation of liver or gall-bladder conditions have been elaborated which offer an increased measure of certainty in the differentiation of normal from disturbed function. In its earliest day, radiology proved a valuable adjunct to the facts of the history and indications of the physical examination in rendering gall stones visible where an adequate amount of radiopaque material was incorporated in the concretion. The great increase in the scope of the method deriving from the application of halogenated phthalein dyes[3] selectively eliminated into the gall bladder has made the procedure one of precision, particularly when the stomach also is rendered visible by barium sulphate[4] and the fluoroscope is freely used.

Finally, by the use of the Rehfuss tube[5] direct access to the duodenum and collection of its contents has become possible. The various chemical methods for the quantitative estimation of the constituents of the duodenal collections developed by McClure and his associates[6] gives a large amount of objective information as to the biliary function of the liver.

With standardized methods of proven worth for the determination of the several factors involved, the data have been collected from a consecutive series of cases in which they have been employed.

All of the patients in the series have been carefully studied by an elaborate diagnostic program, described in detail elsewhere,[7] and the underlying etiology of each adequately established. The selected cases have been drawn from a much larger consecutive series which may broadly be divided into two major etiologic groups, namely: (*a*) Those presenting primary evidence of disturbed endocrine function, and (*b*) those demonstrating liver and gall-bladder disease without ductless glandular involvement. In the endocrine group, the hepatic disorders appear as complications and the relative frequency may be estimated by comparison of the total number of each endocrine group with that of the series with intercurrent liver disorders. Twenty-one per cent of the thyroid cases showed an hepatic complication, while in the pituitary and ovarian groups the incidence was respectively 2 and 2.5 per cent.

Obviously, liver dysfunction is associated with thyroid disorders with significant frequency, a fact already recorded.[7] Its frequency of occurrence in pituitary and ovarian disease indicates its casual character in these conditions. In the nonendocrine series, liver or gall-bladder disease appeared in 26 per cent of the group, but this datum lacks the authority of the endocrine figures, as a number of known liver cases are included which were selectively received for study.

The composition of the entire group, each patient in which gave definite evidence of an hepatic dysfunction, may be most compactly presented in tabular form.

TABLE I.—COMPOSITION OF GROUP.

Etiologic group.	Sex.		Total
	Male.	Female.	
Not endocrine	51	117	168
Thyroid	18	40	58
Pituitary	2	11	13
Ovary	0	9	9
Pancreas	3	0	3
Pluriglandular	1	0	1
Totals	75	177	252

Three cases of bronzed diabetes and one pluriglandular case with hepatic complication are included in the table as they occurred in the series. For the sake of simplicity in presentation, they will be omitted from the subsequent discussion.

One-third of the group has some endocrine defect; the remainder are primarily liver cases. As might have been anticipated, the thyroid cases dominate the group, being two and a half times as numerous as all of the remaining endocrine cases. The male and female distribution is the same as in the much larger series from which the cases are drawn.

While each of the patients in the group presents a primary condition, many of them exhibit intercurrent disease states which can independently influence the function picture. The determination of these secondary features always forms an essential part of the diagnostic program. A review of the more significant complications is collected in Table I *a*.

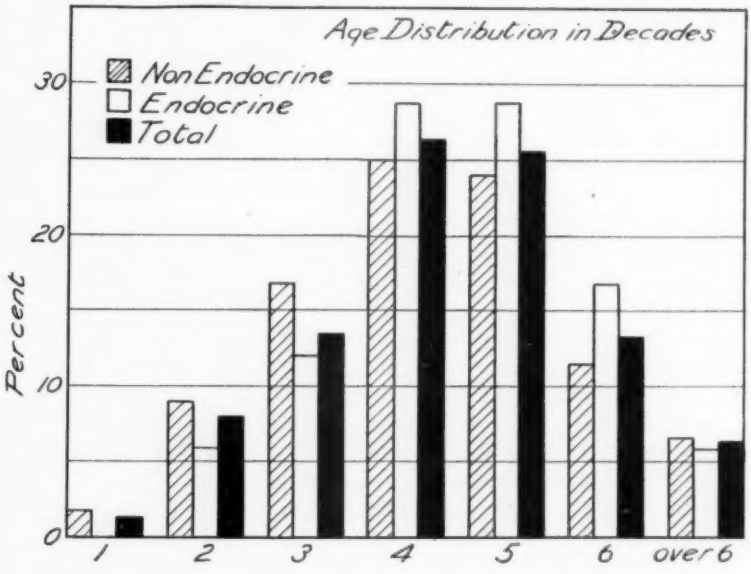
TABLE I *a*.—COMPLICATIONS.

Condition	Not endocrine.	Thyroid.	Pituitary.	Ovary.	Total.
Allergy	4	1	0	1	6
Arthritis	14	5	0	2	21
Focal infection	40	12	1	0	53
Psychoneuroses*	21	6	2	2	31
Cardiorespiratory disorders	41	9	1	2	53
Cancer*	4	1	0	0	5
Lesions of central nervous system*	5	1	1	0	7
Skin diseases	5	0	1	0	6
Syphilis*	10	1	0	0	11

* Frequently influences galactose tolerance independently.

Several of the states, as noted above, may exercise an independent influence on carbohydrate metabolism, and in any complete survey due allowance must be made for them. With uncomplicated syphilis, nerve lesions, and cancer, a lowered tolerance is a common finding. The psychoses and neuroses exhibit the same tendency but in lesser degree.

The age distribution of the patients composing the group is diagrammatically presented in the accompanying graph.



The differences between the endocrine and nonendocrine cases are hardly of significant amount. Over half fall in the fourth and fifth decades, the balance of the remainder in the third and sixth.

Attention to the liver is frequently first attracted by significant reports in the history of the individual patient. A selection of pertinent symptoms has been made and the frequency of report determined.

TABLE II.

	Hepatic group.					Control group.	
	Not endocrine, per cent.	Thyroid, per cent.	Pituitary, per cent.	Gonad, per cent.	Total.* per cent.	Not endocrine, per cent.	endocrine, per cent.
Headache . .	63	69	38	89	64	56	51
Vertigo . . .	37	48	23	44	39	30	28
Jaundice . . .	21	29	31	22	24	6	8
Nausea . . .	41	33	46	0	37	21	20
Vomiting . .	38	24	46	55	35	18	17
Flatulency . .	45	33	38	44	42	16	17
Constipation .	51	48	54	55	50	41	31
Diarrhea . .	6	9	15	0	6	4	3

* Weighted for group representation.

For purposes of control, the data have also been collected from two groups of 500 patients each, representing severally endocrine and nonendocrine conditions. All active liver cases have been excluded, the report of jaundice, as given in the table, recording only a fact from the past history.

Inspection of the data shows the correlations to be excellent between the two series in the hepatic group. Further, these cases show a higher incidence of all of the symptoms listed than does the control group. Even so common a complaint and one of such numerous origins as headache shows a somewhat lower frequency in the nonhepatic controls. Nausea and vomiting are twice as frequently reported in the liver cases, and flatulency shows an even higher incidence. The symptomatic liver picture would seem to be well defined.

Certain other pertinent facts are found in the operative history, the physical examination, and in certain of the objective findings. A number of these have been abstracted from the original individual records and are collected in the next table.

TABLE III.—MISCELLANEOUS DATA.

Data.	Not endocrine, per cent.	Thyroid, per cent.	Pituitary, per cent.	Ovary, per cent.	Total, per cent.
Operative history:					
Cholecystectomy	10	9	0	11	9
Appendectomy	28	26	38	56	29
Other laparotomy	19	3	31	67	17
Physical examination:					
Abdomen tender	33	29	54	44	34
Gall bladder +	15	9	15	0	13
Liver enlarged	7	14	0	11	8
Urine:					
Bile test +	4	2	0	0	6

Nearly 1 in 10 of the patients had had an earlier cholecystectomy. In the writer's experience, gall-bladder disease is always associated with disturbed hepatic function, although the converse does not necessarily hold. Indirect sequelæ from laparotomies performed for purposes other than cholecystectomy cannot be wholly ruled out. In the present series over 1 in every 3 had had some form of abdominal operation.

Tenderness in the upper abdomen was shown by 1 in every 3 of the patients, and careful examination disclosed physical signs of gall-bladder disease in nearly one-seventh of the group. In addition, 8 per cent showed hepatic enlargement of significant proportions. In their entirety, this group of clinical findings offer presumptive evidence of liver and gall-bladder disease in one-half of the patients under consideration.

Only 6 of the group showed bile in the urine, an active icterus being a most infrequent feature of the present series. The icteric index and van den Bergh tests were performed only irregularly, and

the results, while supporting qualitatively those here reported, are too incomplete to warrant numerical presentation.

As noted in the introduction, radiographic study offers authoritative information concerning the gall-bladder status. The visualization of stones in simple Roentgen ray study, the clear-cut evidences of disease yielded by the Graham method and its modifications, and the demonstration of defects of the duodenal cap during a gastrointestinal investigation, give direct information of the greatest importance. The results obtained in the group under consideration are given in the next table.

TABLE IV.—RADIOGRAPHIC DATA.

Data.	Not endocrine.	Thyroid.	Pituitary.	Ovary.	Total.
Combined Graham:					
Number	60	12	8	6	86
Per cent positive	67	58	75	67	66
Gastrointestinal series:					
Number	57	9	7	3	76
Per cent positive	26	33	14	33	26

About one-third each had either a modified Graham[4] or a gastrointestinal study, with the results as given in the table. A small additional number gave direct evidence of cholelithiasis by direct radiography.

While the roentgenologic study yields information about the gall bladder, and thus in the positive cases indicates indirectly the presence of disturbed liver function, the examination of the duodenal contents gives direct evidence of the hepatic status. Several constituents are quantitated and the results interpreted in terms of criteria derived experimentally from the study of a series of normal controls. As the method is of recent origin and as yet not of widespread application, these standards of normality, as experimentally determined, may be given for purposes of comparison.

TABLE V.—LIVER FUNCTION STANDARDS.

Test.	Low normal boundary.
Furfurol index	80
Cholesterol	30
Pigment A (alcohol-soluble)	8
Pigment B (alcohol-insoluble)	7

Of the above, only the cholesterol has reasonable claim to the status of a chemical entity, and even this is by no means certainly established. The furfurol index measures presumptively the so-called bile acids, while the two pigments "A" and "B" are probably mixtures of chromogenic substances differentiated only by their relative solubility in alcohol. Taken together and compared with normal criteria, they constitute a very definite means of determining the biliary level of hepatic activity. The results of applying this method to two-thirds of the entire series under investigation are collected in the next table.

TABLE VI.—LIVER FUNCTION. (MCCLURE.)

Data.	Not endocrine, per cent.	Thyroid, per cent.	Pituitary, per cent.	Ovary, per cent.	Total.	
					No.	Per cent.
Number of cases	109	40	9	4	162	65
Color:						
Brown	22	22	22	25	36	22
Yellow brown	16	23	22	0	28	17
Yellow	62	55	56	75	98	61
Furfurol index below normal	83	78	78	100	133	82
Cholesterol below normal	57	55	44	75	91	56
Pigment A (alcohol-soluble) below normal	62	50	44	75	95	59
Pigment B (alcohol-insoluble) below normal	64	40	56	75	94	58

The furfurol index seems to be most sensitive of the several indicators of hepatic derangement, while the color (yellow to yellow-brown) of the collected material comes next in order. The three other indices show substantially the same degree of response in delicacy, though the actual figures vary among themselves in the several subgroups. Determination of disordered function rests upon the combined data of the individual case. The great majority of those examined gave a weight of evidence warranting the conclusion of definite dysfunction, though naturally the degree of disturbance varied from slight to severe.

Weighing the evidence available from all sources, only a portion of which have been discussed in this paper, the final conclusion as to the liver status may be reduced to numerical expression.

TABLE VII.—STATUS OF LIVER AND GALL BLADDER.

Condition.	Not endocrine. No. cases.	Thyroid. No. cases.	Pituitary. No. cases.	Ovary. No. cases.	Total No. cases.
Hepatic dysfunction:					
Established	152	57	12	9	230
Probable	16	1	1	0	18
Pathologic gall bladder:					
Established	56	20	6	4	86
Probable	4	4	1	1	10

"Established" cases are those in which actual positive objective evidence is available to support the diagnosis. "Probable" cases are those in which a number of confirmatory data are present but which lack, for one or another reason, the final crucial observation. These latter are less than 10 per cent in the liver group, and about that magnitude in the gall-bladder series. As might be anticipated, the cases with gall-bladder complications are but a fraction of the whole.

The liver function test gives direct evidence only of the level of biliary activity, but the long series of pathologic cases studied in the elaboration of this method[6] warrants the inference that with biliary activity depressed, other hepatic function levels—though not necessarily all—are likewise affected.

With hepatic dysfunction established or probable in all, and associated gall-bladder disease in practically 40 per cent, attention may next be turned to the galactose tolerance.

Only a few words of general information concerning this quantity are necessary. The tolerance meal is that dose administered under conventionally defined conditions which will produce the transitory appearance of sugar in the urine in amounts detectable by a delicate qualitative reagent. Equally, doses 10 gm. less in amount yield uniformly negative urines.

An attempt to quantitate by microchemical methods all of the reducing substances in the urine, and then, on the basis of their fermentability to report them as either glucose or galactose, possibly adds to the sensitivity of the test, but certainly does not enhance its accuracy. Glycuresis, the "carbohydrate paradox," and the presence of assimilable but unusable carbohydrate substances as impurities in the test sugar, as noted by Folin and Berglund,[8] and others, introduce factors of complication which cannot be resolved by the simple expedient of fermentation with the interpretation of the unfermented portion as galactose. In a 30-gm. dose every 0.1 per cent of impurity potentially puts 30 mg. of reducing body of unknown composition into the urine. Only by quantitative isolation of the entire mass of reducing substances, identification of the several compounds and the quantitative estimation of each of them as individual chemical entities, could further light be thrown on the mechanisms involved. And even then the uncertainties engendered by the carbohydrate paradox would not be eliminated.

The fact remains, based upon the study of over 4000 individuals, that, with a given person, a certain dose of the purest obtainable galactose administered under uniform standardized conditions will produce an elimination of galactose—verified by osazone, mucic acid formation and other objective methods—in amount yielding a clear-cut positive test, while the dose 10 gm. less in quantity will not. Attempts to refine the test would undoubtedly bring into consideration the disturbing influence of other mechanisms, variations in which are now absorbed by the simple procedure advocated.

The normal dose for the male is 30 gm. throughout the life span, the immature female responds to 20, in a state of sexual rest, during maturity, to 40, and after the menopause exhibits a tendency, not uniformly expressed, to decline to 30 gm.

As has been shown in papers previously cited,[1,7] disturbance in the function levels of the several endocrine glands modify the galactose tolerance in no uncertain way. Posterior lobe and thyroid failure tend to raise the assimilation limit, though not in like degree; equally, overactivity of the posterior pituitary and the thyroid, together with ovarian failure, depress the galactose tolerance, but again with definite quantitative differences. Further, a variety

of conditions not demonstrably associated with ductless glandular activities apparently have the power of decreasing appreciably the tolerance limit.

Turning now to the observations in the present series, the collected data are given in the next table.

TABLE VIII.—GALACTOSE TOLERANCE.

Etiologic group.	Diminished.		Normal	Increased.	
	No.	Average amount, per cent.		No.	Average amount, per cent.
Not endocrine:					
Female	70	−53	12	6	+58
Male	38	−50	6	2	+33
	108		18	8	
Thyroid:					
Female	27	−48	5	2	+33
Male	13	−54	4	0	
	40		9	2	
Pituitary:					
Female	4	−50	1	6	+81
Male	0	...	0	1	+133
	4		1	7	
Ovary:					
Female	6	−38	0	1*	+50
Grand totals	158		28	18	

* Castrate.

Of the 44 cases with no report on galactose tolerance, 34 not endocrine, 7 thyroid, 2 ovary, and 1 pituitary, the three-day requirement for the test was the inhibiting factor. Most of them showed sugar in the urine, indicating a probable though not wholly certain lowering of the galactose tolerance.

Considering first the endocrine subgroups, the thyroid cases show a marked downward tendency to the sugar tolerance. All but 3 of them were cases of hypothyroidism, a condition that produces an upward trend to the assimilation limit. The 3 hyperactive cases showed a characteristic lowering, but so did 37 of the failures. In the group[9] showing normal levels it seems probable that either the liver disturbance had not affected greatly the carbohydrate metabolism or that the two opposing influences had compensated each other. In the 2 cases showing a slightly increased level, the upward tendency produced by thyroid failure has seemingly overweighed the opposing influence of the liver derangement.

The 4 pituitary cases with lowered tolerance were of the dysfunctional type and could be caused as well by the endocrine as by the liver condition. The 1 case with normal tolerance was a bilobar failure, and the normal level could represent a mutual compensation of opposing forces. All 7 of the cases with raised tolerance had

posterior lobe failure. It has long been recognized that this condition increases the assimilation limit of carbohydrate in a most marked degree. While all 7 were demonstrated liver cases, the pituitary influence outweighed the common liver effect, and the summation produced an increase of no uncertain proportions.

The ovarian group shows several highly interesting features. Of the 7 with the galactose test reported, 1, a castrate, showed an increased level for this condition. Surgery left no doubt as to the endocrine status, the liver function test gave only traces of the several constituents, and a later operation disclosed well-marked cholecystitis with numerous stones. Of the remaining 6, 3 were postmenopausal, and all were reduced to—but not below—the level of marked gonad failure (20 gm.) as produced by disease or castration. In other words, the endocrine state was sufficient to determine the recorded lowering of the sugar tolerance, and the liver derangement—demonstrably severe in at least half of the group—caused no further depression.

To summarize then, while the majority of the cases show a definite downward tendency or offer reasonable explanations for normal or increased tolerances, a few records, primarily in the ovarian group, suggest the possibility of another, though less frequent, effect of hepatic dysfunction on the sugar tolerance.

Turning now to the larger series in which endocrine disease plays no part and liver disorder is the basic condition, the majority (81 per cent) of those tested show the anticipated depression of the galactose assimilation limit. Twenty-six cases, however, either show no effect or actually present an increase. While the posterior pituitary is the most powerful known agent producing an increase, other factors may come into consideration. A more detailed survey of these cases without endocrine complication is warranted and is presented in the next table.

TABLE IX.—ANALYSIS OF CASES WITH NORMAL OR INCREASED TOLERANCE.

	Normal.		Increased.		
	Female.	Male.	Female.	Male.	Total.
Total number	12	6	6	2	26
Possible modifying factors:					
Postmenopause	6	..	1	..	7
Diagnosis from operative history	3	1	0	0	4
Function test only weakly positive	2	0	0	0	2
Total, doubtful cases	11	1	1	0	13
Function tests and other evidence ++	1	5	5	2	13

Six of the group with normal and one with increased tolerance (women) can be tentatively eliminated as their classification rests on the assumption that 30 gm. is the postmenopausal level. Actually 20 per cent of the normal women in this condition earlier reported[1]

showed a level of 40 gm. On this basis, the 6 cases at 30 could be regarded as showing a slight depression, while the 1 case at 40 could change status to the normal group.

Four of the patients derived their hepatic status from a history of earlier cholecystectomy. It is possible to infer that earlier liver damage had been corrected—at least so far as the carbohydrate metabolism is concerned.

Two of the normal cases gave function tests that were only weakly positive, and again, the inference is warranted that the derangement was not of sufficient magnitude to produce detectable changes in the sugar test.

Renal factors of sufficient magnitude to lower permeability and thus apparently raise tolerance were demonstrably absent from the group. Deleting the cases which conventionally may be called doubtful, there yet remains 6 with normal tolerance (or 7 if the one postmenopausal female be added) and an equal number with tolerances significantly increased. All of these gave definite objective evidence of clear-cut hepatic involvement of an established severity. In short, in 4 per cent of the established liver cases a normal, and in an equal number an increased sugar tolerance is found. That a second mechanism or an opposite modification of the common formula is involved would seem to be a warrantable conclusion. Its nature and mode of operation are at present entirely obscure although plausible speculations could be numerous. The fact is recorded for two reasons, first, to aid in the interpretation of galactose tolerance tests as a part of an objective diagnostic program, and second, to emphasize once more that the regulation of the carbohydrate metabolism is influenced by other agents than the function level of the islands of Langerhans even though this be the prototype of all regulatory forces.

Conclusion and Summary. 1. A number of case records from a long series of carefully studied patients have been selected on the common basis of hepatic dysfunction. These have been analyzed from the standpoint: (*a*) of the evidences supporting the initial diagnosis; (*b*) the presence of possible complicating disease conditions; (*c*) the combined effect on the assimilation limit for galactose of the agencies active in the individual case.

2. It has been shown that while the general tendency of liver disease is to depress the galactose tolerance, a certain number of cases is found in which an apparently uncomplicated liver derangement is associated either with normal or even increased power to utilize this sugar. A new mechanism or new modification of the common effect is suggested by the data.

NOTE.—In conclusion the authors wish to express their grateful thanks to their colleagues, Drs. Charles W. McClure and George Levene, together with their associates, for the extensive contributions which they have made to this work in the duodenal testing and radiographic investigations respectively.

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THE SPECIFIC THERAPY OF PNEUMOCOCCUS TYPE I AND TYPE II PNEUMONIA.*

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The present report is concerned with the results obtained by the use of a concentrated solution of pneumococcus antibodies, at the New York Hospital, during the four winters 1926 to 1930. During this time a carefully controlled series of cases was studied. The cases to receive treatment were determined by numerical sequence, thus eliminating any element of selection and providing a series of control cases. The concentrated solution contained antibodies only for pneumococcus Type I and Type II. This was prepared according to the method of Felton[1] and was supplied through Dr. W. H. Park of the New York City Board of Health. Only cases of pneumonia due to these two types of pneumococci are included in this report. The following table shows the mortality in the treated and control series:

Control series.				Treated series.			
Type.	Cases.	Died.	Mortality, per cent.	Type.	Cases.	Died.	Mortality, per cent.
I	20	5		I	19	1	
II	29	15		II	35	9	
	49	20	40.8		54	10	18.5

Upon analysis of the above table it is evident that the number of cases in each group is not large, but evenly distributed and the

* The cases reported were from the First Medical Division, in charge of Dr. Lewis A. Conner and the Second Medical Division, in charge of Dr. William R. Williams.

differences in the results obtained in the treated, as compared with those in the control series are sufficiently striking to lend considerable weight. Among 19 treated Type I cases there was but one death, as opposed to 5 deaths in 20 control cases. Among 35 treated Type II cases there were 9 deaths, as compared with 15 deaths in 29 control cases. As a result of this therapeutic experiment, conducted over a period of four years, a mortality of only 18.5 per cent occurred in the treated series containing both Type I and Type II pneumococci as opposed to 40.8 per cent in the control series.

In the cases due to the pneumococcus Type I, the use of the concentrate has met with marked success clinically as well as statistically. Following adequate dosage the patient usually looks and feels better; very often the temperature shows a decided drop and the pulse rate becomes slower. It is not unusual apparently to abort the disease when treatment is started soon after the onset. On the other hand, following a favorable reaction in the temperature and degree of toxemia, the temperature may rise and then fall again after additional therapy. This alternate rise and fall of the temperature curve is quite characteristic of the specific therapy of pneumococcus Type I pneumonia and indicates the importance of continuing the therapy until the temperature has definitely remained normal and other signs of activity in the pneumonic lung, such as the expectoration of typical bright bloody sputum, have disappeared.

There has been a tendency to undervalue the importance of specific therapy if the duration of the disease previous to treatment has been more than four to five days. This is not in accord with our experience, where very seriously ill cases treated late have responded well. The presence of bacteremia in pneumococcus Type I pneumonia, regardless of whether it occurs early or late, is a serious finding and limits the prognosis accordingly. In these cases large amounts of antibody solution are necessary, and usually effective. A further discussion of dosage will follow.

In considering the results of the treatment of pneumococcus Type II pneumonia the statistics here reported are favorable. During the past four years only 9 deaths have occurred in 35 treated cases, compared with 15 deaths in 29 control cases. It is also important to add that whereas only 2 cases of Type II bacteremia have recovered without specific therapy, during this period, 7 cases have recovered under treatment with the Type II concentrate.

Clinical observation of the cases of pneumococcus Type II pneumonia treated with the concentrate has confirmed the statistical results. While it is not often possible definitely to abort the disease, as in the case of pneumococcus Type I, it has been our experience that the patients feel better, are less toxic, and usually have some reduction in the degree of pyrexia following treatment. Here, as in Type I pneumonia, specific therapy should be instituted and continued as long as evidence of active infection is present. A

positive blood culture in pneumococcus Type II pneumonia is of the gravest prognostic significance and calls for the administration of large quantities of concentrate at frequent intervals.

Since the most convincing evidence of the efficacy of Type II concentrate lies in its effect on bacteremia, 4 charts are presented of patients with this complication which illustrate the method of dosage and the results obtained.

In the following case active therapy was started with a polyvalent concentrate containing 1000 units of pneumococcus Type II antibody in the presence of a bacteremia totaling 15 colonies per cubic centimeter. After 30,000 units had been administered the blood culture was sterile. A remarkable drop in temperature, accompanied by a corresponding diminution in pulse and respiration rates, occurred following the administration of 82,000 units during a period of twenty-four hours.

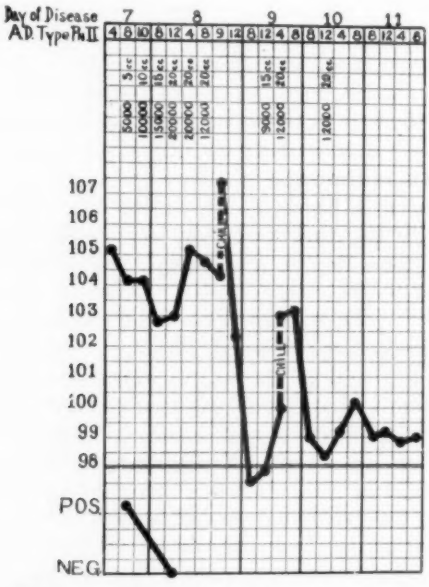

FIG. 1.—Case I. Temperature and blood-culture chart of a case of pneumococcus Type II pneumonia with bacteremia treated on the seventh day. Blood culture sterile after the administration of 30,000 units of Type II concentrate (Felton).

CASE I (Fig. 1).—A. D., male, Italian, aged twenty-two years, was admitted to the hospital on the seventh day of his illness with frank signs of consolidation in the upper right lobe. The patient was very toxic and delirious. Blood was taken for culture, and 5000 units of pneumococcus Type II antibody were administered. Two hours later 10,000 units were given. The following morning the temperature had dropped 2° and clinical improvement was manifest. Treatment was started at 8 A.M., and four intravenous injections given. The last injection was of a different

preparation from that used in the preceding injections, and the administration of 20 cc. was followed by a chill, the temperature rising to 107°. The next morning the temperature was 97.6°; respiration, 18; pulse, 64. On that day 21,000 units were given and 12,000 units on the next day. Blood culture taken before treatment showed 15 colonies per cubic centimeter. The next blood culture, taken sixteen hours later, was sterile. During the first twenty-four hours of treatment a total of 70,000 units of pneumococcus Type II antibody was received. The patient recovered.

The next report illustrates a case of bacteremia where recovery followed the administration of a moderate amount of antibody solution.

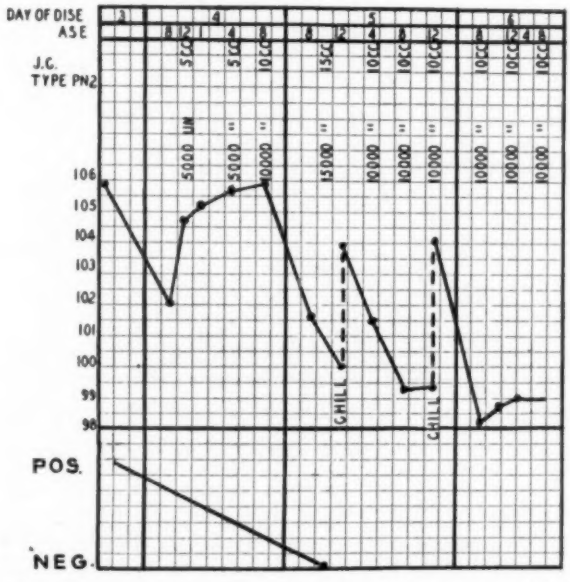

FIG. 2.—Case II. A case of pneumococcus Type II pneumonia with bacteremia. Following the administration of 20,000 units of Type II concentrate (Felton) the temperature had fallen and the blood culture was sterile.

CASE II (Fig. 2).—J. C., male, laborer, aged thirty years, was admitted to the hospital on the third day of his illness. On admission blood culture and sputum typing showed pneumococcus Type II, and signs were present in the left lower lobe. On the fourth day of his illness he received three intravenous injections of pneumococcus Type II antibody, totaling 20,000 units. The following morning the temperature had dropped to 101.6°. After the fourth injection of 15 cc., comprising 15,000 units, a chill occurred. Three doses of 10,000 units each were given during the balance of the day, and following the last dose the patient had another chill. Because of the initial positive blood culture and the high rate of mortality associated with this finding, treatment was continued on the sixth day, although the temperature was then normal, the patient being given three doses of 10,000 units each.

The following case illustrates a much more severe course than the one just cited. In this instance the blood culture, shown to be positive on two occasions preceding therapy, became sterile following the administration of 195,000 units of the concentrate.

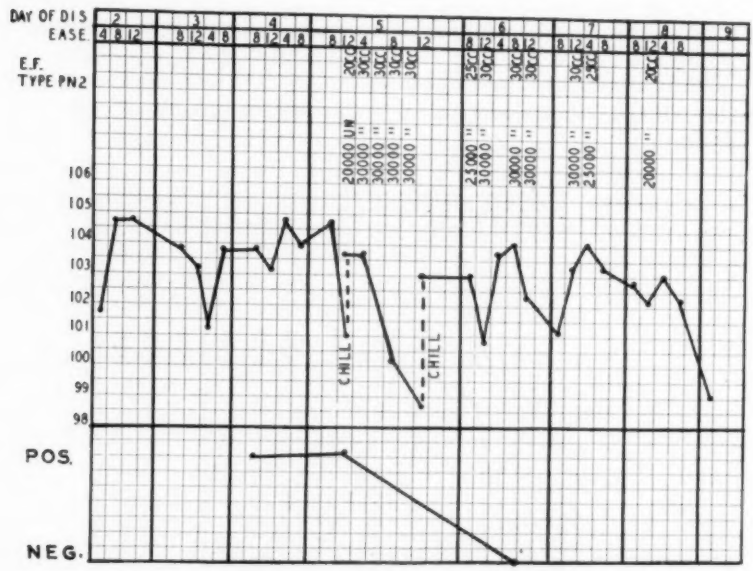

FIG. 3.—Case III. A very severely ill case of pneumococcus Type II pneumonia with bacteremia present on two consecutive days preceding specific therapy. Following the administration of 195,000 units of Type II concentrate (Felton) the blood culture was sterile.

CASE III (Fig. 3).—E. F., male, Italian, aged thirty-two years, was admitted to the hospital on the second day of the disease, with very early signs of pneumonia in the left lower lobe. On the fourth day blood culture was positive for pneumococcus Type II. This was reported on the morning of the fifth day, and when the first dose of 20 cc., containing 20,000 units of Type II antibody, was given a blood culture was taken which was also positive. During the fifth day five intravenous injections were given, one of 20 cc. and four of 30 cc. each, totaling 140,000 units. Two chills occurred which were not alarming. On the sixth day the blood culture was sterile. Notwithstanding the fact that the temperature remained high, the toxemia was less severe. Four doses of antibody were given, totaling 115,000 units. On the seventh day two doses, totaling 55,000 units, were given. On the eighth day, although the patient was obviously much better, 20,000 units were given. The temperature fell by crisis, and convalescence was uneventful.

The following case illustrates a fourth one of pneumococcus Type II pneumonia and bacteremia, treated with large amounts of antibody concentrate followed by a favorable result. Here the persistence of bacteremia in the face of the daily administration of over

140,000 units of the concentrate indicates strikingly its severity in connection with cases of pneumococcus Type II pneumonia. It is probable that in this case without the aid of specific therapy the number of organisms in the blood stream would have quickly increased, causing death from sepsis.

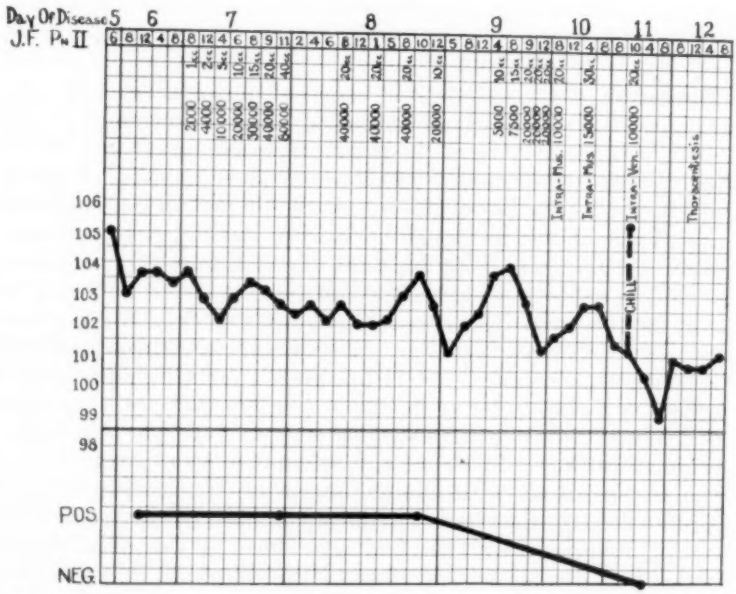

FIG. 4.—Case IV. A very severely ill case of pneumococcus Type II pneumonia with bacteremia which persisted for two days in spite of the administration of over 140,000 units of Type II concentrate per day. With continuance of treatment blood culture became sterile. Complicated by hypersensitiveness to horse serum and the development of empyema.

CASE IV (Fig. 4).—J. F., female, Porto Rican, aged thirty-five years, was admitted to the hospital on the fifth day of her illness with signs of consolidation in the left upper and lower lobes. Blood culture was taken the day following and the sputum was typed. On the seventh day of her illness the blood culture was reported positive for pneumococcus Type II, to the extent of 3 colonies per cubic centimeter, in both broth bottles and in the agar plates. At this time the patient was coughing up copious amounts of thick, rusty sputum, and respiration was accelerated and shallow; she was wildly delirious, and after moving about in bed there were heard beginning râles of pulmonary edema. Because of a moderately positive skin reaction to horse-serum, treatment was started with very small doses.

Using a monovalent Type II antibody concentrate containing 2000 units per cubic centimeter, the patient was given 196,000 units within the next fifteen hours. A blood culture taken after 106,000 units had been given was still positive, though to a less extent. On the following day 140,000 units were given. On this day, after 120,000 units, it was possible to demonstrate pneumococci Type II in the broth culture receptacle. On the morning of the ninth day the patient's condition was clinically much

improved, 336,000 units having been administered. On the tenth day, because of the poor condition of the patient's veins, 25,000 units were given intramuscularly. No pneumococci could be demonstrated in the blood stream at this time. On the eleventh day the administration of 10,000 units, intravenously, was followed by a chill, the temperature rising 4°. On the twelfth day a thoracentesis was done, and a serous fluid was aspirated which on culture showed pneumococcus Type II. Three days later intercostal drainage was performed by Dr. C. L. Gibson, and recovery, although slow, was ultimately complete.

Discussion. The therapeutic value of the concentrated anti-pneumococcus serum for pneumococcus Type I pneumonia seems established, not only from the results reported here, but from the work of other investigators, notably Cecil and Plummer,[2] Bullowa,[3] and Finland.[4] The success of the specific therapy of pneumococcus Type II pneumonia has not been so clear cut in the reports mentioned. At the New York Hospital, the sterilization of the blood, the clinical improvement and the statistical evidence following the use of the concentrate in cases of pneumococcus Type II pneumonia have been definitely favorable. The therapeutic efficacy of antibody in pneumococcus Type II pneumonia must be considered in the light of a remedy for an infection so severe that when untreated it is followed by a mortality varying from 31 to 52 per cent (Cole,[5] Cecil and Sutliff[6]). Likewise, any attempt to treat pneumococcus Type II pneumonia with immune serum or its derivatives has to take into account the relative frequency of bacteremia and the high mortality associated with this finding. Thus Cole and his associates found a bacteremia at some stage of the disease in 33.1 per cent, and in these cases the mortality was 73.4 per cent; Cecil, Baldwin and Larsen[7] demonstrated the pneumococcus in 43.3 per cent of their series and in these cases the mortality was 90.3 per cent. Therefore, if it can be shown that the administration of pneumococcus Type II concentrate can sterilize the blood stream and definitely reduce the death rate the evidence in favor of its use is clear. We believe that the work at the New York Hospital during the past four years offers convincing proof of these results following the use of the concentrate.

The answer to the question of dosage in both pneumococcus Type I and Type II pneumonia is one that varies with the severity of the disease. In general, it is believed better to err on the side of administering overlarge than oversmall doses of the concentrate. The procedure usually advised is as follows: As soon as pneumonia is diagnosed, sputum should be collected for typing by the mouse method, and blood for culture should be withdrawn. If the case is seen early and the above procedure carried out, the danger in delaying the administration of antibody until the type is ascertained is, in the great majority of cases, negligible. If the sputum report is pneumococcus Type I or Type II and the blood culture is sterile,

the patient should receive, within the next twenty-four hours, 50,000 to 100,000 units of antibody, intravenously, depending upon the severity of the clinical course. If on the following day the temperature is down and the patient appears clinically much improved, at least 20,000 units should be given in order that the antibody balance and concentration may be maintained. If the temperature remains high and improvement has not resulted, 50,000 to 100,000 units of antibody should be given in the second twenty-four hours, according to the severity of the infection, and a similar dosage maintained until the prognosis of the illness is assured. In pneumococcus Type II pneumonia it is wise to give larger amounts than in pneumococcus Type I pneumonia, other factors being equal. It is helpful to take a blood culture preceding a therapeutic injection each day. The presence of bacteremia in pneumococcus Type I pneumonia is serious and indicates the desirability of giving increased amounts of antibody. In the presence of a pneumococcus Type II positive culture the prognosis is distinctly bad and large amounts of antibody must be administered at frequent intervals. Under these conditions at least 100,000 units should be given in the course of twenty-four hours.

Mention should be made of the obvious advantages of the concentrate prepared according to Felton over whole immune serum. The factor of concentration, expressed in terms of units, is very helpful in fixing the dose and affords greater facility in administration, owing to its smaller volume, the dosage varying from 5 to 30 cc. per dose with the concentrate as opposed to 50 to 200 cc. when whole serum is used. The work of Felton[8] indicates convincingly his ability to make a concentrate 10 to 20 times as strong as the whole serum used as the basis for the extraction, and it is this feature, as indicated by Baldwin and Rhoades[9] in an earlier report, that is essential to the specific therapy of pneumococcus Type II pneumonia. The disadvantages inherent in any modification of whole serum, consisting principally in thermal or chill reactions, are becoming less pronounced. Less than 10 per cent of all injections are followed by chill reactions. On the other hand, serum sickness is largely eliminated, less than 25 per cent of the cases having this complication, and when it does occur it is mild, causing only brief discomfort incomparable in severity with that produced by the use of the whole serum.

Conclusions. 1. The use of pneumococcus concentrated immune bodies in pneumococcus Type I and Type II pneumonia is relatively free from dangerous reactions and serum sickness, and makes it possible to give large amounts of antibody in a short space of time.

2. By using these extracts, favorable clinical results are often obtained, and it seems to be definitely established that with them pneumococcus Type I and Type II bacteremia can be eliminated in many cases and a favorable outcome result.

3. Although the best results are obtained when specific therapy is started early, evidence is given to show that as long as the pneumonic infection appears active, specific therapy is indicated.

4. The specific therapy of pneumococcus Type II pneumonia, hitherto a discouraging procedure, seems to have definite value when concentrates of high unit value are given in large amounts.

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THE MAINTENANCE DOSE OF POTENT MATERIAL IN PERNICIOUS ANEMIA.

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The treatment of pernicious anemia by potent material contained in liver,[1] kidney[2] and stomach[3] has become recognized throughout the world as a useful and very satisfactory procedure since Minot and Murphy[1] first described the effect of feeding liver in this disease. Remissions can also be induced by material rendered available from muscle meat by normal gastric digestion.[4]

Much information has been published concerning the various aspects of treatment necessary to induce remission.[5] The problem concerning the amount of effective substance that these patients should take to maintain them in the best possible state of health, after the concentration of their red blood cells and hemoglobin have returned to approximately normal, has not been so clearly formulated. Although the level of the red blood cells and hemoglobin serves as one important guide to the amount of therapeutic material necessary for the maintenance of health, there are other aspects of each case that should be recognized as important criteria in determining the amount of liver or potent substitute that should be taken. These other matters pertain to the patient's habits, symptoms and physical signs, the presence or absence of complications, and the detailed histology of the blood itself. No remission can be considered complete until the red cells assume normal size and shape, the white blood cells and blood platelets return to normal numbers, and the color index becomes 1 or less.

This paper concerns a study of the maintenance dose of the potent material in liver determined particularly from the level of the hemoglobin and red blood cells following complete or partial remission induced by one or another form of material effective in pernicious anemia. The dosage is expressed in terms of liver extract. Minot and Murphy originally recognized that some patients required greater amounts of potent material than others in order to maintain a normal blood level. Other physicians[6,7] have confirmed this fact. Thus, at Dr. Minot's suggestion, the studies reported here were made in an effort to learn something about the cause of this dissimilarity.

One hundred and eight cases of pernicious anemia in complete or partial remission under treatment in outpatient clinics constitute the material on which the observations are based. We personally observed these cases in the clinics under the supervision of Drs. Minot, Murphy and Castle for a period of ten months and acknowledge our indebtedness for permission to utilize data accumulated prior to our own observations.

Nearly all the patients had the general appearance of health, but examination of the blood sometimes showed a persistent moderate degree of anemia. Each patient attended a clinic at intervals of from two to four weeks when the erythrocytes were counted and the hemoglobin determined; the latter by the Sahli method after our own observations were begun; 4,500,000 red cells per cubic millimeter and 85 per cent hemoglobin were regarded as the lower limits of normal.

Some confusion concerning the dose of potent material appears to have arisen among physicians because preparations of liver have been prescribed as the amount actually taken by the patient. Liver extracts have been prescribed as the amount of whole liver

from which the extract is derived. Most of our cases were treated with Liver Extract, No. 343, N.N.R. (Lilly*). Although the contents of each vial is prepared from 100 gm. of liver, as material is lost in preparation, the actual potency is approximately equal to that of 60 gm. of prepared liver pulp.[8] Prepared raw liver pulp, cooked liver and "domestic extract" (Castle and Bowie,[9]) were used at times for some of our cases, taking into account the fact that in preparing or cooking liver, usually about 25 per cent and sometimes more by weight of liver substance is lost. In the analysis of results, however, the dosage of potent material was expressed always in terms of the number of grams of liver used for the preparation of Liver Extract No. 343. The possibility that different clinical results may be obtained when the same dose of potent substance is given in different forms or ways; for example, as whole liver in contrast to liver extract is recognized but is not for discussion here.

The study of these patients served to demonstrate clearly that the maintenance dose varied for different individuals, but it was possible to make an arbitrary classification of the 108 patients into three rather distinct groups and a fourth special group of 8 cases.

The first group comprised of 64 patients whose red blood cells, except in 5 cases (8 per cent), remained normal in numbers on daily amounts of extract derived from 100 to 400 gm. of liver. However, in these 5 cases when slight relapse occurred, the red cells rose to normal when the patient took extract derived from 400 gm. of liver. In the second group were 31 patients who did not maintain their red cell count satisfactorily when they took, on the average, extract derived from 350 gm. of liver, but whose red cells were maintained at a normal level later, when they took each day amounts of extract derived from 500 to 1000 gm. of liver. The third group was comprised of only 5 patients. Their red blood cells had been brought from a low level to between 3,500,000 and 4,100,000 per c.mm. by liver extract derived from 600 gm. of liver daily, but when they took daily extract derived from 1200 to 1500 gm. of liver and also iron, their red cells did not reach normal numbers. The special 8 cases comprising the fourth group were ones distinctly benefited by iron in addition to liver therapy and are not included in the statistical data given below for the 100 cases of the first three groups.

Statistical study (Table I) shows that the first group of patients averaged fifteen and twenty-four years younger than the patients of Groups 2 and 3 respectively. The "duration of the disease," from the time of symptoms of distinct anemia to the time our personal observations were begun, was on the average twenty-five months for both the first and second groups. The patients of the third group had the disease on an average 10.5 months longer.

* This was made possible through the generosity of Eli Lilly and Company, who have kindly donated a considerable amount of the extract used in carrying out these observations.

However, as there were only 5 cases in this last group, the figure is probably not significant as there were over 14 cases in the first two groups who had had their disease over four years. The average duration of liver therapy for each group was slightly less than the time recorded for the "duration of the disease."

TABLE I.—ANALYSIS OF MAINTENANCE DOSE OF POTENT MATERIAL AND OTHER FACTORS FOR 100 PATIENTS WITH PERNICIOUS ANEMIA.

	Group I.	Group II.	Group III.
Number of cases	64	31	5
Average age, years	45	60	69
Average initial maintenance dosage of effective material, grams*	240	350	450
Average second maintenance dosage of effective material, grams*	...	800	800
Average level of red blood cells in millions per c.mm. on first dose	5.00	3.70	3.85
Average level of hemoglobin, per cent on first dose	94.00	77.60	77.00
Average level of red blood cells in millions per c.mm. on second dose	...	4.60	40.00
Average level of hemoglobin, per cent on second dose	...	87.80	3.83
Per cent with infection	10.92	15.11	77.50
Per cent with arteriosclerosis	4.69	35.48	80.00
Per cent with both infection and arteriosclerosis	3.12	6.45	40.00
Per cent with neuromuscular symptoms	38.19	45.16	80.00
Per cent with neuromuscular symptoms improved	85.74	57.14	20.00

* Expressed in grams of liver from which Liver Extract No. 343 (N.N.R.) is derived.

Further analysis showed that 10.9 per cent of the first group of patients presented some low-grade infection, such as chronic bronchitis or pyelitis or suffered from chronic atrophic or hypertrophic arthritis, and 4.7 per cent had mild arteriosclerosis. Diet and hygiene were in general good. Of the second group, 15.1 per cent had infections, and 35.5 per cent presented at least a fairly pronounced degree of arteriosclerosis, while in the third group 40 per cent had a chronic infection; all had a considerable degree of arteriosclerosis and 80 per cent marked arteriosclerosis, as evidenced by "pipe-stem" arteries.

Neurologic symptoms, including such manifestations as mild paresthesias in the hands and feet, and impaired vibratory sense, especially in the legs, were present in 38.2 per cent of the patients in the first group. Improvement, complete or partial, occurred in 85.7 per cent of these individuals during their treatment with a preparation of liver.

Evidence of some definite neurologic lesion was present in 45.1 per cent in the second group. Of these patients, only 57.1 per cent showed improvement in neurologic disorders during liver treatment, but it is important to note that neuromuscular symptoms decreased after moderate amounts of liver extract were fed and often lessened still more when the larger amounts of potent material were taken.

Four of the 5 patients of Group 3 had varying degrees of com-

bined system disease. In only one did the neurologic symptoms decrease while under treatment.

Since combined system disease did not develop in any of the 108 cases when a normal blood level was maintained, the greater frequency of neurologic changes in the second and third groups may be partly accounted for by inadequate treatment, which is evidenced by the persistence of a reduced red blood cell count over a considerable period of time. Neuromuscular symptoms appeared or grew worse only in patients who did not take a proper amount of potent material as shown by a lapse in the red blood cell level. Similar results have been reported by other physicians.[10, 11, 12] The importance of frequent regular examinations of the blood of all pernicious anemia patients can therefore be stressed on this account alone.

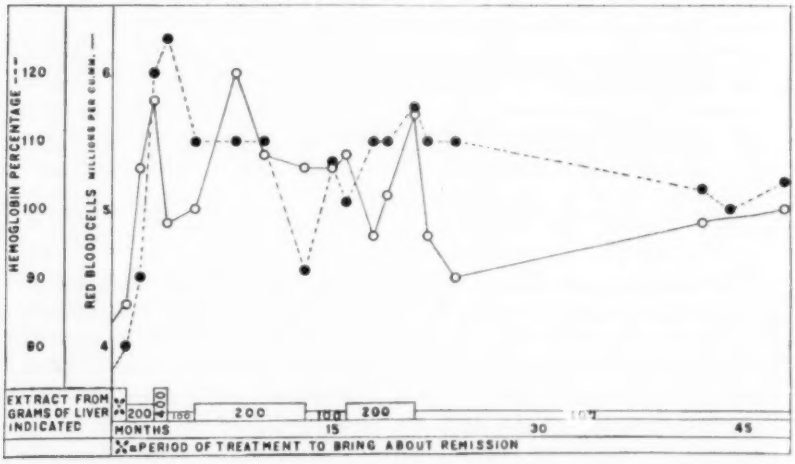

FIG. 1.—Pernicious anemia. Example of case assigned to first group. Red blood cells and hemoglobin remained at normal level for four years while patient took extract derived from 100 to 200 gm. of liver each day.

Figure 1 illustrates a case in the first group. Ninety-two per cent (59 cases) of these patients during the period of observation lasting from a few months to over four years have maintained their red blood cells and hemoglobin (Table I) at normal levels on an average daily amount of potent material equivalent to that in Liver Extract No. 343 derived from 240 gm. of liver. Some of the patients were kept on distinctly small quantities of potent material in an effort to learn whether or not relapses would occur in the course of treatment. This did occur in 5 (8 per cent) cases so that the red cells and hemoglobin decreased below normal (Fig. 2). In each instance the relapse in the state of the blood was mild and occurred after the patient had been taking daily for from eighteen months to three and a half years less potent material on the average than the

amount contained in extract derived from 300 gm. of liver. In these cases a normal red blood-cell level was reëstablished when the patients took extract derived from 400 gm. of liver and they thus approached in character the cases placed in Group 2. It is recognized that whether a case falls into Group 1 or 2 may depend somewhat on how long the patient was observed, because, for example, a patient might maintain for a year a normal red blood-cell level while taking daily extract prepared from 300 gm. of liver and thus be placed in Group 1; but if then, however, relapse developed and double the amount of extract was given while the red cells returned to normal numbers and stayed there the case would fall into Group 2. Such a state of affairs is illustrated by Fig. 5. The groups do serve,

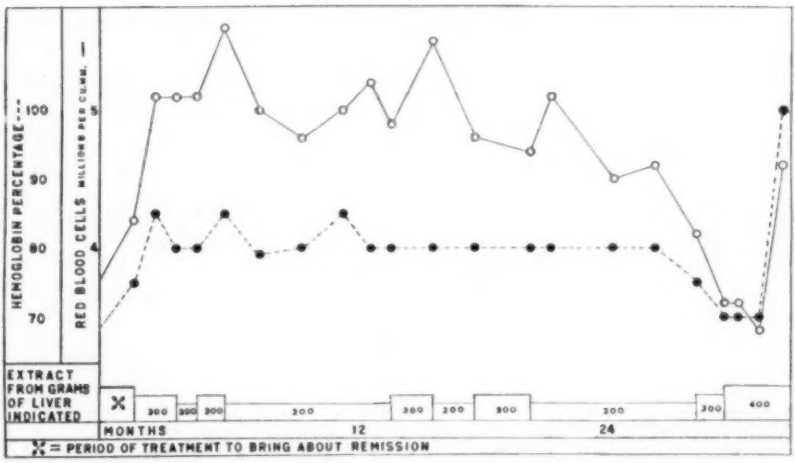

FIG. 2.—Uncomplicated case of pernicious anemia. Blood level remained normal for two years on extract derived from 200 to 300 gm. of liver daily followed by a fall of the red blood cells and hemoglobin. The blood returned to the normal level when liver extract derived from 400 gm. was given daily.

however, to simplify the presentation of the observations concerning the maintenance dosage of active principle.

Isaacs[13] has pointed out that the relapses of pernicious anemia have a tendency to be more frequent in the early spring or to recur at the time of the year the patient first experienced relapse. It is thus plausible to treat patients more intensively at those periods when relapse might be anticipated. It is highly desirable that patients should take regularly greater amounts of effective substance than just sufficient to maintain a normal blood level. Fig. 2 illustrates this point for after somewhat over two years, without change in dosage and without evidence of complications, this patient developed a mild relapse. From such cases it appears that the maintenance dose may need to be increased in some instances as

time elapses, or that if such patients had taken more liver with regularity, an optimal rather than a minimal quantity, a relapse might have been averted.

It is to be recalled that before the days of liver therapy, if excellent remissions took place a high blood level often was maintained for many months and rarely for years. Thus, it cannot be stated precisely how much influence small amounts of liver may have in maintaining a high blood level in such cases as recorded in Fig. 2.

Figures 3, 4 and 5 give examples of the state of affairs for the 31 patients in the second group, or those individuals who required a relatively large amount of potent material to maintain a normal blood level. The case recorded in Fig. 3 was one of a man who, while taking daily liver extract derived from 300 gm. of liver for

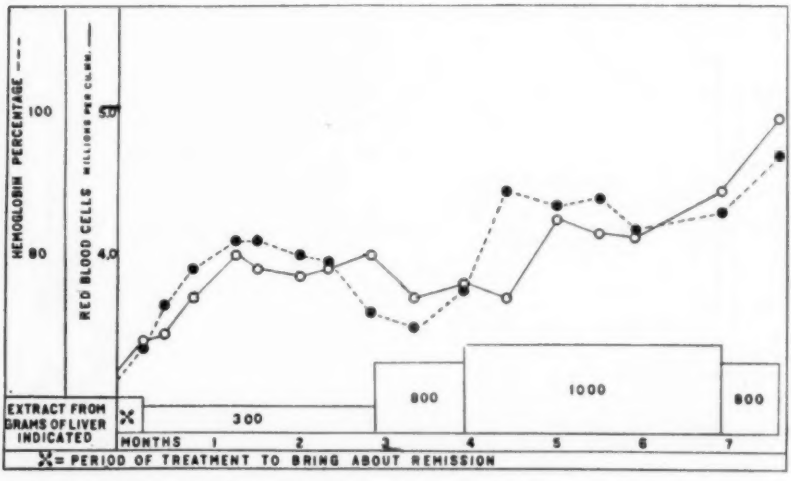

FIG. 3.—Uncomplicated pernicious anemia. The relative ineffectiveness of small daily amounts of liver extract contrasted with the effectiveness of large amounts each day.

three months, showed an unusually sluggish rise of erythrocytes to 4,000,000 per c.mm. and hemoglobin to 80 per cent. He improved further when the amount of liver extract was approximately tripled. After five months on this larger dose the red blood cells and hemoglobin reached the normal level. Aside from moderate arteriosclerosis this patient had no complications.

Figure 4 illustrates the uncomplicated case of a woman, aged sixty-three years. She had been observed for three and a half years during which time anemia reappeared twice. On each occasion her maintenance dose of potent material had been reduced to an amount that apparently can maintain the red blood cells of some cases at a normal level. The figure illustrates the facility with which relapses occur when the dosage of potent material is inadequate.

Figure 5 records an instance where for almost eighteen months apparently a sufficient quantity of liver extract was taken to maintain the red blood cells and hemoglobin at approximately normal levels and if the case had not been observed for more than this period of time it would have been placed in Group 1. The mild relapse was soon overcome by doubling the dose of liver extract, but when the amount was decreased to a quantity that formerly appeared to maintain an appropriate blood level, relapse ensued to be followed by remission when greater amounts of extract were taken. Cases of this sort, like many others, must be considered in the light of experiences before liver therapy was known when "spontaneous" remissions of various lengths were prone to occur. Table I gives

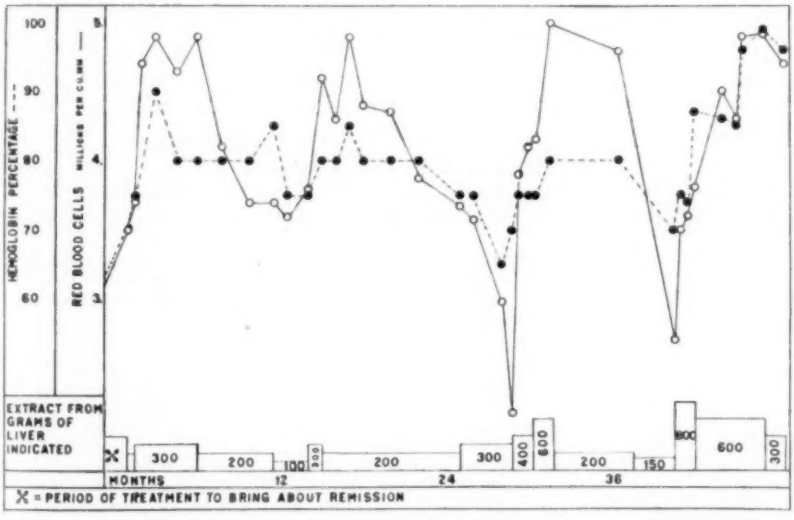

FIG. 4.—Uncomplicated pernicious anemia. Case shows relapses on daily doses of extract derived from 100 to 300 gm. of liver. Prompt remissions when the dose of liver extract was increased.

the results of increasing the dosage of liver extract in cases where the maintenance dose was inadequate. Although on the average the increased daily dose was extract derived from 800 gm. of liver the data must not be interpreted as indicating that the optimal dose for many of these cases was so large. There is evidence at hand that extract prepared from 600 gm. of liver is ample for many of these cases given larger amounts.

The part played by infection in rendering a patient partially refractory to the potent substance contained in liver is illustrated by Fig. 6. This case of typical pernicious anemia was one of a woman, aged sixty-two years, who had been under treatment for three years, during which time she also suffered from severe chronic

atrophic arthritis with acute exacerbations. Her red blood cells were not restored to the normal level during this period, in spite of the daily administration of liver extract, which, often for many consecutive weeks, was as much as that derived from 600 gm. of liver. Subsequent to a month of hospital treatment, her arthritis was much improved; and then amounts of liver extract previously

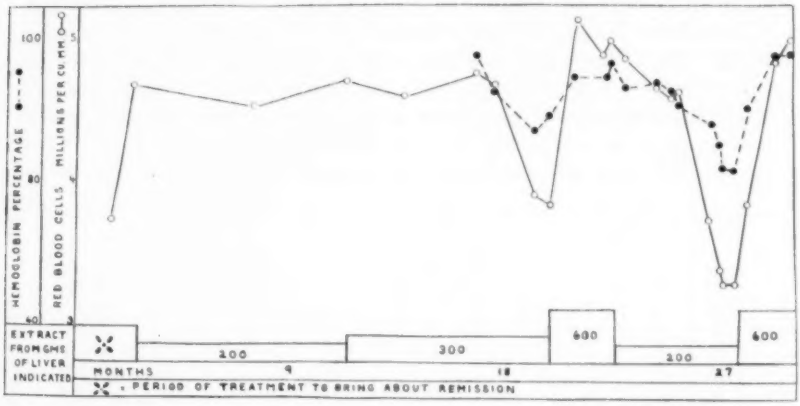

FIG. 5.—Uncomplicated pernicious anemia. Blood level not maintained on liver extract daily obtained from 200 to 300 gm. of liver, although at first there was no fall within eighteen months. Red blood cells and hemoglobin raised on two occasions by approximately tripling the dose of liver extract.

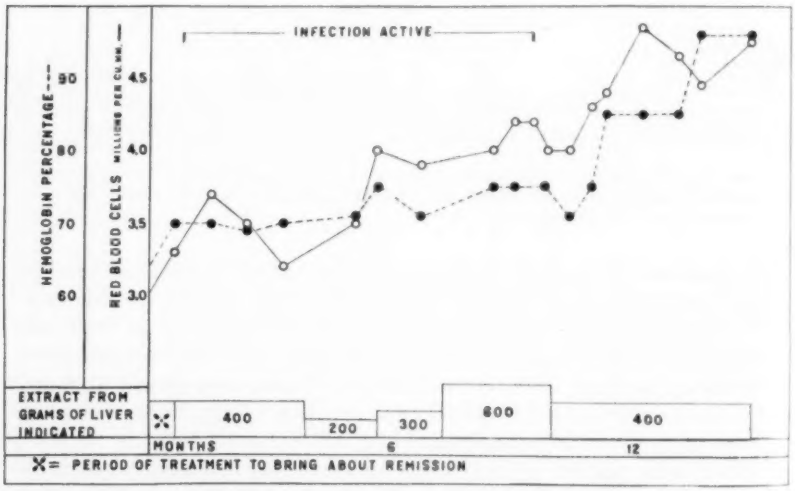

FIG. 6.—Pernicious anemia complicated by atrophic arthritis with acute exacerbations. Large doses of liver extract were ineffective in raising the red blood cells and hemoglobin to normal levels while the infection was active. With subsidence of infection the blood level became normal on daily doses of liver extract derived from 400 gm.

inadequate permitted the number of red cells and hemoglobin to rise to normal.

The 8 patients placed in the special fourth group (Table II), separate from the other 100 cases, had responded rapidly to liver therapy, but were unable to increase their hemoglobin and red blood-cell count to normal even when treated with large amounts of the active principle contained in liver; but they did so rather promptly when iron was taken as iron and ammonium citrate, in doses of from 4 to 6 gm. daily. These patients did not seem to have the characteristics of the cases of Group 3, discussed further on, in which liver and iron alleviated the patient only partially of anemia. A history of chronic dietary deficiency of one sort or another was obtained for each of the 8 cases and 3 had a chronic infection and arteriosclerosis. Patients with a blood picture of so-called secondary anemia, due to certain sorts of defective diets, often respond well to large doses of iron.[14,15,16] It thus seems that these cases at first thought to be somewhat refractory to liver therapy probably had what may be termed a doubled deficiency, in that iron as well as the active principle effective in pernicious anemia was needed to raise their red blood cells to a normal level and apparently to maintain them there.

TABLE II.—PATIENTS BENEFITED BY IRON IN ADDITION TO LIVER THERAPY.

Number of cases	8
Average age, years	52
Average initial maintenance dosage of liver extract before iron, grams*	700
Average second dosage liver extract when iron also was given, grams*	500
Average level of red blood cells in millions per c.mm. on liver extract alone	4.01
Average hemoglobin, per cent on liver extract alone	72.00
Average level of red blood cells in millions per c.mm. on liver extract and iron	4.53
Average level of hemoglobin per cent on liver extract and iron	89.00
Per cent with infection	37.50
Per cent with arteriosclerosis	37.50
Per cent with infection and arteriosclerosis	25.00

* Expressed in grams of liver from which Liver Extract No. 343 (N.N.R.) is derived.

Figure 7 illustrates this type of case of pernicious anemia in a female with a history of little or no meat, fruit, or green vegetables in the diet for years. Her blood was not restored to the normal level even by extract derived from 1200 gm. of liver daily. After the daily addition of 6 gm. of iron and ammonium citrate and a reduction in liver extract to the amount derived from 400 gm. a day, distinct improvement occurred not only in her blood, but also in her general health.

Another type of anemia other than that characteristic of pernicious anemia may develop in pernicious anemia patients not only from dietary deficiencies, but also from other causes such as chronic bloodloss. Thus two distinct types of disordered blood

formation may occur in the same patient. This took place in several of our cases. An unusual opportunity to observe the influence of bloodloss in a patient with pernicious anemia has been made by Dr. Minot, who has furnished us kindly with his data for publication here. The data are synopsized in Fig. 8. This patient when acutely ill received in three days Liver Extract No. 343 (N.N.R.) derived from 5000 gm. of liver. This was followed on the sixth day by a maximal rise of the reticulocytes and by normal convalescence. A normal red blood-cell level was maintained for about 1.5 years on material taken daily equivalent to liver extract derived from 400 gm. of liver. There followed a period when the patient was not seen for some time because he traveled extensively, during

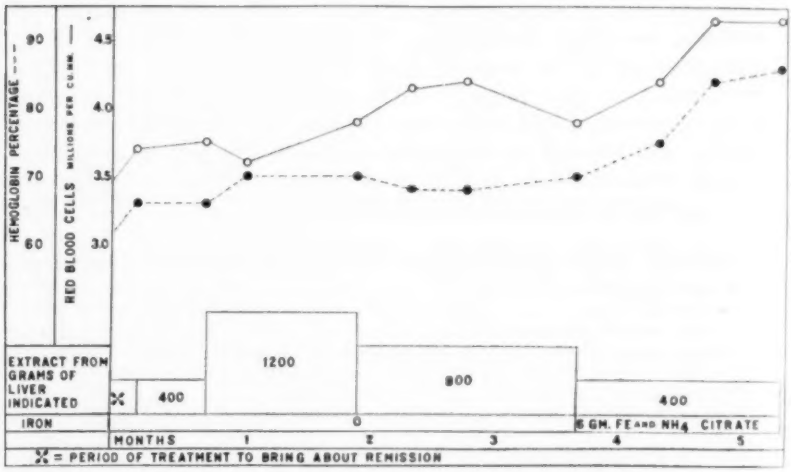

FIG. 7.—Pernicious anemia with a diet poor in meat and green vegetables. Incomplete response to large amounts of liver extract. When iron and ammonium citrate was given, although the dosage of liver extract was reduced, the concentration of the red blood cells and hemoglobin became normal.

which time he obtained an unsatisfactory diet. However, he continued to take daily the same amount of potent material. During this period he lost very frequently small amounts of blood from hemorrhoids, so that distinct anemia with a low color index appeared which is in contrast to the high color index before liver therapy. The hemorrhoids were removed and bleeding stopped, but his red blood-cell level failed to return to normal on his customary amount of liver extract. He was then given 6 gm. of iron and ammonium citrate daily. His reticulocytes responded and there followed a rapid return of the red blood-cell count and hemoglobin to normal.

In addition to the 95 patients of Groups 1 and 2 and the 8 cases treated with a liver preparation and iron whose blood was brought to normal and maintained there when suitable amounts of materials

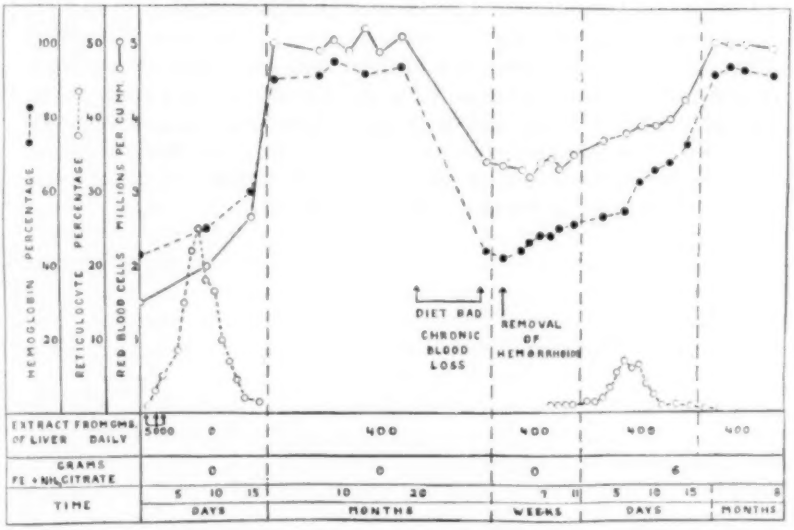

FIG. 8.—Case of pernicious anemia complicated by chronic bloodloss. Normal remission following extract from 5000 gm. of liver given over a period of three days. Blood remained at normal level while the patient took extract from 400 gm. of liver daily for twenty months. Fall in red blood cells and hemoglobin during ten months in spite of extract from 400 gm. of liver daily when his diet was deficient in meat and green vegetables and when he experienced bloodloss from hemorrhoids. With cessation of bleeding very slow response on liver alone but a reticulocyte rise occurred, and prompt return of blood to a normal level when 6 gm. of iron and ammonium citrate were given daily in addition to extract from 400 gm. of liver. Note the high color index before liver therapy and the low color index when anemia due to bloodloss developed.

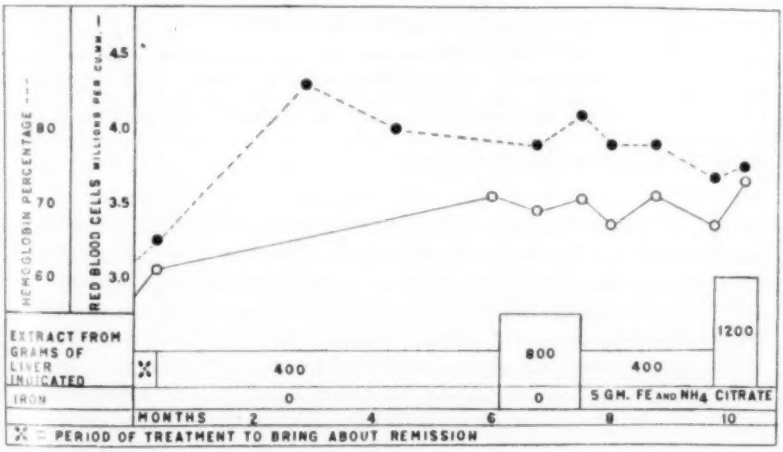

FIG. 9.—Pernicious anemia complicated by severe arteriosclerosis. Example of type of patient assigned to third group. Blood counts remained subnormal on increasing amounts of liver extract and iron.

were fed and pronounced infection or complications were absent, there were 5 cases, Group 3, which remained somewhat refractory. Although liver kept them in a state of remission large doses with or without iron did not cause their red blood cells and hemoglobin to reach normal levels and thus the anemia was not completely banished. Average data for 5 cases are of little significance, but it is perhaps noteworthy that the average age of these patients was greater than those in Groups 1 and 2 (Table I).

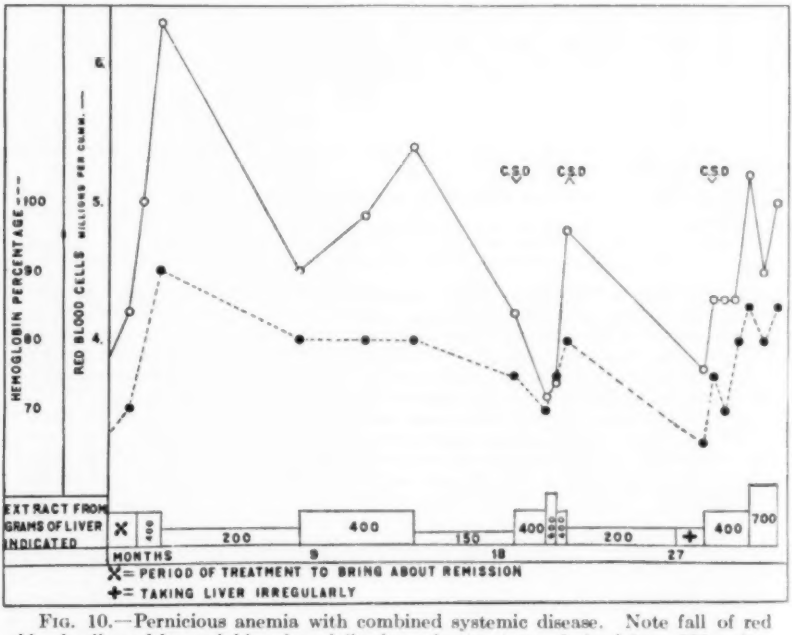

FIG. 10.—Pernicious anemia with combined systemic disease. Note fall of red blood cells and hemoglobin when daily dose of extract was derived from 200 or less grams of liver. When the dose was increased the red blood cells and hemoglobin promptly rose. Exacerbation of combined systemic disease occurred at periods when red blood cells and hemoglobin were lowest.

Two of these 5 cases were complicated by a definite infectious process and one had chronic nephritis. Four of the patients had a very pronounced degree and 1 an insignificant degree of arteriosclerosis. A chronic pyelitis existed in the latter. Fig. 9 is an illustration of the course of 1 of the 5 cases.

The giving of inadequate amounts of liver or of potent substitute is by far the commonest cause for treated patients with pernicious anemia failing to remain in at least fair health. They must be observed frequently and properly advised following repeated scrutiny of their blood and all aspects of each case. The physician must insist that the patient take the amount of material prescribed

with regularity, and this amount should be optimal, not a minimal quantity.

Figure 10 illustrates the case of a patient who need not have suffered so much if proper amounts of material had been taken. This patient had mild early symptoms of combined system disease when first treated. Inadequacy of liver dosage conditioned a relapse. At the same time the neurologic signs became more severe. With increased amounts of liver his blood improved and the spinal cord symptoms lessened. This dose was not maintained and another relapse occurred with a simultaneous increase in the nervous manifestations. Improvement took place only when large amounts of liver again raised the red blood-cell level to normal. During each exacerbation of the anemia the combined system disease advanced.

The reason for the varying degrees of response to the same amount of potent material has not been explained adequately, but it is comparable perhaps to what occurs in disorders arising from vitamin or internal secretion deficiencies.[17] Bone-marrow exhaustion unless due to an extraneous cause, appears to play no part since the response to larger doses of liver usually is prompt. Many complications, such as infections, may inhibit the influence of effective material and can play a rôle in the ease with which the patient responds to treatment. One must also not forget that two causes for anemia may exist in the same patient. The part played by an abnormal condition of the vascular system, especially arteriosclerosis, in affecting tissue metabolism has been little emphasized. Minot[18] has suggested that it may act to precipitate certain deficiency diseases and hinder the influence of the substance effective in pernicious anemia.

Analysis of our results showed that while, of the cases in Group 1, only 4.69 per cent had arteriosclerosis, 35.5 per cent of the Group 2 and certainly 80 per cent of the Group 3 patients presented this complication. Such a wide divergence may possibly suggest at least one of the reasons for the different responses of the three groups.

It is possible that different responses to the same amount of potent material depend occasionally on the patient's ability to absorb or assimilate the effective substance from the intestinal tract, or for their stomachs to utilize the necessary material from the food. This point is being studied in this laboratory and may be clarified by the use of a potent extract given intravenously.[19]

It is obvious that the best therapy consists in giving patients an ample quantity of an effective substance, if they are to remain in as satisfactory a state of health as possible. Minimal quantities may permit them to remain on a borderline where untoward symptoms and signs can easily develop. This point has been stressed particularly in reference to food deficiencies and by Minot in reference to pernicious anemia. The series of 108 cases reported here

were relatively unintelligent patients of low economic status. Thus, on the one hand, it was frequently difficult to get the patients to appreciate the importance of taking regularly the material prescribed, so that periods occurred when some patients took little or none of the active principle, and, on the other hand, an effort was made to have the patients waste no liver substance. Thus, too often these patients, as shown especially by those of Group 2, did not receive optimal quantities.

Indicative of the value of a relative excess of liver substance as a maintenance dose is Minot's and Murphy's[20] experience, which we are privileged to mention here, with a group of about 40 private patients followed for over three years. About 85 per cent of these cases correspond to the first group of our series and only about 15 per cent fall into our other groups. Thus, very few patients showed a tendency to relapse. This may be explained by the fact that the great majority of this group of patients have been taking daily potent material equivalent to that in extract derived from 400 gm. or more of liver and none less than the amount contained in extract derived from 300 gm., which is in contrast to the patients we studied whose customary daily dose of liver extract was usually less than the amount derived from 400 gm. of liver.

It therefore seems evident that patients with pernicious anemia should be observed frequently and their health maintained as well as possible, not with a minimal amount of potent material but with an optimal quantity, which will vary considerably for different cases.

Summary. One hundred and eight patients with pernicious anemia have been studied in an effort to determine the maintenance dose of liver or potent substitute. One hundred cases were placed in three groups and 8 composed a fourth special group, as follows:

Group 1. Sixty-four patients whose red blood cells continued to remain at a normal level when they took only relatively small amounts of effective substance. These patients were treated for the same amount of time as those in Group 2.

Group 2. Thirty-one patients who required large amounts of effective material to maintain a normal blood level.

Group 3. Five patients whose red cells remained about 20 per cent below normal even when very large amounts of potent liver material and iron were fed.

Group 4. Eight patients whose red cells and hemoglobin remained somewhat below normal when large amounts of liver extract were taken, but who obtained a normal blood level when iron was given with even a smaller amount of liver extract than formerly.

Observation of the latter group, together with the study of a case in which chronic bloodloss occurred, indicates that two sorts of disordered blood formation may occur in a patient with pernicious anemia.

The rôle played by infections and other complications in inhibiting the effect of potent material is mentioned.

The importance of arteriosclerosis in conditioning the response to liver therapy is suggested, because the average age of the patients and the incidence of arterial disease in the first three groups progressively increases; that is to say, a larger maintenance dose was required usually when arteriosclerosis was present.

The patients whose red blood-cell level remained normal on the smaller amounts of liver, or potent substitute, showed on the average the greatest improvement in the function of their neuromuscular system. Thus, neuromuscular symptoms decreased less, as a rule, when arteriosclerosis or other complications were present. These symptoms only appeared or grew worse when the red blood-cell level lapsed, or the patient took insufficient amounts of liver or potent substitute.

It is evident that some patients require a much larger maintenance dose of potent material than other patients. Optimal quantities of an effective substance to keep patients in as satisfactory a state of health as possible should be prescribed, rather than amounts that permit them to remain in a state where untoward events can develop easily. The daily maintenance dose is "*not some liver but enough liver for the given case.*"

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I. ANEMIA OF DOGS PRODUCED BY FEEDING OF THE WHOLE ONIONS AND OF ONION FRACTIONS.

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Technical Assistance by D. Lindsay.

(From the Research and Biologic Laboratories, Parke, Davis & Co.)

In the course of verifying the results of Sebrell[1] on the "anemia of dogs produced by feeding of onions," we became interested in the study of the fraction of onions which was responsible for the anemia.

Experimental. Fresh Spanish onions were peeled and ground fine through a food chopper. A part of the ground onions was autoclaved at 120° C. for half an hour. A part of the autoclaved onions were pressed through a fruit press, yielding 10 cc. of onion juice for every 15 gm. of fresh onions used. Adult dogs of mixed breeds were maintained on a complete nutrient diet. The onions were fed to dogs daily in 15-gm. doses per kilogram of body weight. The onion juice was given daily in 10-cc. quantities per kilogram of body weight, equivalent to 15 gm. of fresh onions. The effect of onions or their fractions was determined by the changes produced in the blood picture, as reported by Sebrell. The blood samples were taken in the morning before the feeding of the dogs. The blood examination consisted of the red cells, white cells and reticulocytes, the hemoglobin and hematocrit determinations. The hemoglobin was estimated by Sahli method, using the Hellige colored prism attachment, calibrated 17 gm. equal 100 per cent hemoglobin and equivalent to 80 per cent hemoglobin by Sahli method.

Four dogs were used on each fraction of onions. All dogs reponded uniformly to the feeding of rough, autoclaved whole or onion juice. In Table I the results of only one dog in each group are given. The effect of feeding either rough or autoclaved onions or their juice to dogs was extremely uniform and striking. The maximum drop in the red cell count occurred on the seventh to eighth day following six feedings with 15 gm. of rough onions or equivalent amount of autoclaved onions or their juice. Simultaneously with the hemoglobin and red cell decrease, the white cell count increased. Though new and immature red cells were thrown into the circulating blood stream soon after the commencement of feeding with

onions or their fractions, the outpouring of reticulocytes occurred four to six days following the last feeding. The lowest hemoglobin value was 20 per cent and red cell count 1,200,000. In every case following the maximum red cell destruction the dogs developed tolerance to fresh or autoclaved onions or their fraction, and further feeding had no effect on the blood elements.

TABLE I.—AN EFFECT OF ROUGH AND AUTOCLAVED ONIONS OR THEIR JUICE IN ANEMIA OF DOGS.

Days.	Dog No. 17. Rough onions.				Dog No. 18. Autoclaved onions.				Dog. No. 23. Autoclaved onion juice.		
	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c.	Reticulocytes, per cent.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c.	Reticulocytes, per cent.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c.
0	91*	7.76	10,900	0.0	103*	7.72	7,200	0.2	83*	6.28	6,300
5th	50	4.80	22,000	0.5	61	4.10	21,600	2.0	70	4.10	19,200
6th	32†	2.38	26,000	2.0	45†	3.05	22,000	3.0			
7th	30	1.99	25,000	3.0	35	2.52	23,900	4.7	52	3.68	26,500
8th	28	2.40	32,000	2.2	31	1.70	31,000	7.5	41†	3.38	23,100
10th	32	2.51	21,000	17.0	40	2.78	41,000	20.0	37	2.24	30,100
12th	45	2.80	4,800	10.0	54	3.12	15,700	27.0	42	3.08	20,900
14th	50*	3.60	6,900	5.7	63*	3.68	9,900	9.3	55*	3.26	17,200
17th	50	4.02	7,400	4.0	63	4.52					
19th	56	4.28	11,200	3.5	63	4.86	6,100	...	71†	4.96	10,800
21st	58†	4.16	11,000	3.0	71†	5.24	8,600				

* Blood examination on the day before the feeding.
† Last feeding with onions.

Our results on feeding onions to dogs entirely confirmed Sebrell's results that onions rough or cooked produce severe destruction of red cells in dogs. The feeding of onion juice produced equally severe anemia. The animals, after a certain period of feeding, established tolerance to onions or their juice.

The feeding of rough or cooked onions or their juice necessitated the use of considerable volume. An attempt was made to dry the autoclaved onion juice *in vacuo* at 50° C. for twenty-four hours. This resulted in a dry, crisp residue without pungent odor of onions, but distinct onion taste. One gram of this dry material was equivalent to 17.5 cc. of the autoclaved onion juice and 0.57 gm. of this dry material, equivalent to 10 cc. of the onion juice per kilogram of body weight, was fed daily to dogs. Two dogs were placed on the dried material and two on the onion juice.

The dogs on the onion juice showed maximum hemoglobin reduction with the seventh feeding, while the dogs on the dried onion juice had not reached the maximum hemoglobin reduction with twelve feedings. This relation was found in both dogs fed with dried material. It is evident that the dried material was not as active as the onion juice itself.

Another lot of ground fresh Spanish onions was subjected to a steam distillation in an attempt to collect the oil of onions. The distillate equaling 1 cc. to every 2 gm. of fresh onions, was fed to three dogs in 7.5-cc. to 15-cc. doses per kilogram body weight. The residue from the distillation was fed to one dog. The dogs received for the first seven days 7.5 cc. of the distillate per kilogram of body weight; during the remaining four feedings the dose was doubled to 15 cc. per day per kilogram. The residue of the distillation was fed 15 gm. per kilogram daily for twelve days.

TABLE II.—AN EFFECT OF DRIED ONION MATERIAL OBTAINED BY DRYING THE ONION JUICE IN VACUO AT 50° C. FOR TWENTY-FOUR HOURS.

Days.	Dog No. 25. Autoclaved onion juice.				Dog No. 24. Autoclaved onion juice dried *in vacuo* at 50° C.			
	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c.	Hematocrit, per cent.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c.	Hematocrit, per cent.
0	75*	5.86	21,700†	42.5	101	7.28	6,200	53.2
3d	64	4.56	24,800	41.4	90	6.82	8,600	46.8
5th	47	3.85	29,800	35.1	72	5.28	9,600	44.4
7th*	23‡	1.62	45,000	..	63	4.74	14,600	38.4
8th	22	1.56	62,000	13.5	62	4.32	19,200	32.7
10th	24	1.90	56,000	14.0	65	4.36	19,400	33.7
12th	30	2.08	26,500	24.0	55‡	3.60	18,000	36.8
14th	41	2.86	27,900	26.3	58	3.80	11,300	33.3
18th	63	4.08	14,900	31.6	82	5.65	7,400	45.0

* Blood examination on the day before feeding.
† Dog's blood count suggested a respiratory disease.
‡ Last feeding.

TABLE III.—AN EFFECT OF FEEDING THE STEAM DISTILLATE AND THE RESIDUE OF ONIONS TO DOGS.

Days.	Dog No. 26. Steam distillate.				Dog No. 34. Steam residue.				Dog No. 31. Onion juice.			
	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c.	Hematocrit, per cent.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c.	Hematocrit, per cent.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c.	Hematocrit, per cent.
0	76*	6.54	17,220†	47.4	81*	750	10,000	42.0	92*	7.60	12,300	56.3
3d	68	6.30	10,900	42.9	81	745	11,000	42.3	77	7.04	19,500	50.0
5th	67	6.68	9,800	..	..	..	..	..	82	8.80	12,300	46.7
7th	77‡	7.70	10,200	43.3	82	730	11,900	42.5	83	6.40	21,500	44.9
9th	75	6.30	8,700	42.6	..	..	..	..	71°	6.26	25,600	41.0
12th	75°	6.23	12,600	50.7	73°	730	11,900	40.0	34	2.42	35,000	24.0

* Blood examination on the day before feeding.
† Dog probably with respiratory disease.
‡ Dosage doubled.
° Last dose.

The feeding of the steam distillate and the residue from the distillation of onions, as noted in Table III, caused little or no change in the blood constituents in dogs, although the distillate possessed extremely strong odor of onions and the dogs were more unwilling to take it than the onion juice or the fresh onions. The control, Dog No. 31, responded promptly to feeding of onion juice.

Discussion. The mode of the action of onions or their juice upon the animal organism, leading to severe anemia, is not established. It appears that hemolysis plays a considerable part in the red cell destruction. Following the third or fourth feeding the blood serum becomes tinged red with hemoglobin. At the lowest level of hemoglobin values or red cell counts, the serum becomes dark red in

color. The blood smears taken at the stage of maximum red cell destruction show considerable fragmentation of red cells. The urine of these dogs becomes deep dark brown in color.

Summary. The feeding of rough or autoclaved onions or their juice to adult dogs results in severe anemia and in this respect the results are entirely in agreement with those of Sebrell. The onion juice dried was less effective than the juice itself. The steam distillate of rough onions and the residue of the distillation possessed little or no activity.

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II. ANEMIA IN DOGS PRODUCED BY FEEDING DISULPHIDE COMPOUNDS.

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In the previous paper we confirmed the results of Sebrell[1] that onion feeding to dogs produced severe anemia. We also found that certain fractions[2] of onions when fed to dogs produced a similar anemia. This led us to believe that the action was due to the oil of onions. Since the allyl propyl disulphide, which is recognized as the main constituent of oil of onions, was not available, a series of chemically related compounds were studied, all of which possess the disulphide linkage –S–S–. The n-propyl disulphide $CH_3CH_2CH_2$–S–S–$CH_2CH_2CH_3$, and the benzyl disulphide, $C_6H_5CH_2$–S–S–$CH_2C_6H_5$ were chosen as typical representatives in which the sulphur is in aliphatic grouping. The di-p-tolyl disulphide, $C_6H_5(CH_3)$–S–S–$C_6H_5(CH_3)$ was chosen as a representative in which the sulphur grouping is directly on the benzene ring. The l-cystine was included in this study as representative of sulphur linked to an amino-acid group. This selection covers the field of the disulphide compounds possessing the general formula, R–S–S–R, in which R represents either aliphatic or aromatic radicals or derivatives of such radicals containing an acidic group.

Experimental. Adult dogs of mixed breeds were maintained on a complete nutritive diet. The drugs were given to dogs in gelatin capsules. The blood samples were taken in the morning before the feeding of the dogs. The blood examination consisted of the red cells, white cells and reticulocytes, the hemoglobin and hematocrit determinations.

The *n-propyl disulphide* is an oily substance possessing a strong odor of onions. It was given to four dogs in 1-cc. quantities, from 0.067 to 0.122 cc. per kilogram of body weight, usually following the feeding in the afternoon.

TABLE I.—N-PROPYL DISULPHIDE EFFECT IN ANEMIA OF DOGS.
Dog No. 35.

Date.	Treatment, cc.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c., thousands.	Reticulocytes, per cent.	Hematocrit, per cent.	Weight, kilos.
Sept. 19	1.0*	97	7.28	9.0	0.10	49	12.9
22	1.0	60	4.76	14.0	0.05	33	12.5
24	1.0†	32	3.06	18.0	0.46	21	
25	...	23	1.95	29.8	17.20	17	11.8
26	...	19	0.78	32.0	16.40	20	
27	...	20	1.81	21.2	15.50	13	
29	...	28	2.27	20.6	19.20	19	11.7
30	...	29	2.20	25.9	...	20	
Oct. 1	1.0*	32	2.60	19.0	9.30	22	
2	1.0†	30	...	...	...	...	12.4
3	...	27	2.18	17.8	9.60	21	
4	...	25	1.97	18.7	4.30	19	
6	...	26	2.37	...	12.20	24	
7	...	31	2.67	16.4	11.10	23	
8	1.0*	37	2.90	10.8	9.90	25	
9	1.0	31	3.01	15.1	11.30	21	
10	1.0	28	3.08	23.0	7.00	23	
11	1.0	25	2.69	36.0	...	23	
13	1.0	27	2.68	32.0	10.10	22	
14	1.0	29	...	...	16.40		
15	1.5†	32	...	...	14.00		
16	...	25	2.56	33.1	13.50		
17	...	25	2.38	32.2	15.60	24	12.4
18	...	25	2.55	22.2	15.50	23	
20	...	34	3.19	14.3	13.70	29	
23	...	55	4.00	18.2	5.90	37	12.6
27	1.0*	60	5.26	9.9	3.30	40	
30	1.0	48	6.20	19.4	0.30	40	
Nov. 1	1.0	32	4.32	21.6	5.40	32	
3	0.5	23	2.29	34.8	18.10	25	12.8
4	0.5	22	1.84	36.4	17.0	20	
5	0.75	24	2.06	30.0	23.50	22	
6	0.75	25	2.40	29.0	27.30	23	
7	0.75	27					
8	0.75	26					
9	1.0	29					
12	1.0	28	2.80	17.6	15.00	27	13.3
20	1.0	28	2.75	25.5	24.00	29	

* Feeding started following the blood examination.
† The last feeding.

The effect of n-propyl disulphide on the blood constituents of normal dogs is summarized in Table I. The feeding of the dogs daily for four to six days with the n-propyl disulphide resulted in a severe anemia, and if continued long enough the hemoglobin values dropped below 12 and the dogs usually would die (Fig. 1). In parallel with the lowering of the hemoglobin, the red cell counts dropped. The white cell count rose rapidly and reached a level several times higher than the normal count. A rapid

red cell destruction was followed by an outpouring of young and immature red cells. Discontinuation of n-propyl disulphide feeding reversed the blood picture. The hemoglobin and red cells rapidly increased, while the white cells and reticulocytes decreased. The blood changes induced by n-propyl disulphide closely paralleled those following onion feeding except that the animals did not develop tolerance to n-propyl disulphide. The blood elements could be maintained at a certain level with a proper dose of the drug for over two months. An increase of the dosage was followed with an increased destruction of red cells and a corresponding response of other cell elements.

A repetition of a course of treatment with n-propyl disulphide after the blood regeneration had reached close to the normal level (Table I) was followed with a severe anemia, as if the animals had never been treated before, that is, the animal showed no development of tolerance under a repeated periodic feeding with n-propyl disulphide.

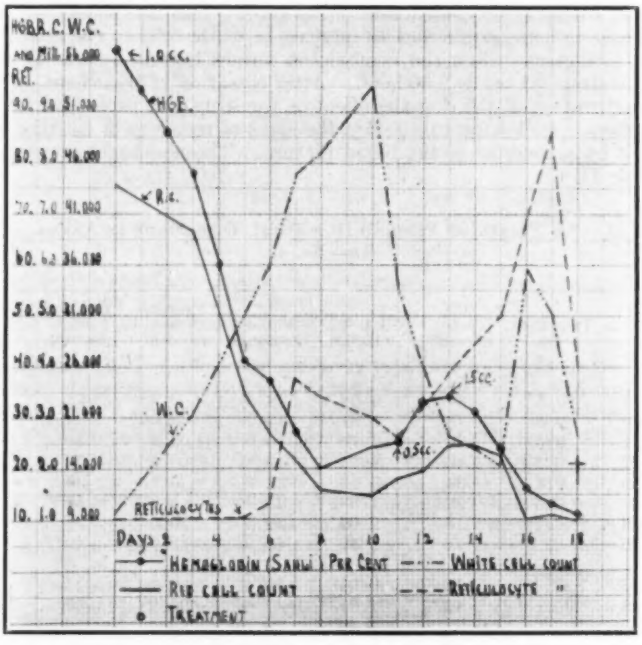

FIG. 1.—N-propyl disulphide in anemia of dogs.

The hemolytic effect of n-propyl disulphide leading to death of the animal from exhaustion of the hemopoietic system is illustrated above. A daily feeding of 1 cc. to Dog No. 42 caused the hemoglobin and red cell number to fall precipitously. Interruption of the feeding for four days led to a mild regenerative effort of the blood elements which continued on an upgrade, even following the administration of 0.5 cc. of n-propyl disulphide for two days. The blood regeneration, however, was checked by an administration of 1.5 cc. of the drug, and if continued on this dose daily the red cells were reduced to 1,000,000 in three days, with the hemoglobin around 15 per cent and death of the dog a few days later with hemoglobin at 11 per cent.

The white cell count rose quickly and uniformly in response to the administration of n-propyl disulphide and increased from normal of 9000 to over 53,000 per c.mm. The reticulocytes and normoblasts began to appear as early as on the third day. The outpouring of reticulocytes occurred with an increased destruction of the red cells, and when the total count of red cells reached about 1,000,000 the reticulocytes and normoblasts constituted over 86 per cent of the total red cells.

The action of the drug appears to be directly upon the circulating red cells without the interference with the erythropoietic centers. The outpouring of young and immature erythrocytes is probably not directly related to the drug, but is a compensatory response similar to that following a severe hemorrhage.

The *di-p-tolyl disulphide*, an aromatic synthetic derivative, is a crystalline substance without an odor. It is insoluble in water, but takes the appearance of an oil at near body temperature. When fed to animals in ½- to 1-gm. doses (32.5 to 99.4 mg. per kilogram of body weight) per day, it was followed with a rapid destruction of red cells. This was accompanied with a decrease in hemoglobin and an increase of white cells. The reticulocytes began to increase when the hemoglobin values became below 30 and the red cells dropped below 2,000,000. After cessation of treatment on a complete saturation of the dog the effect of the drug was prolonged for about three days. Following this period the signs of recovery of the dog became evident by a reversal of the blood picture. These changes are illustrated in Table II.

TABLE II.—AN EFFECT OF FEEDING DI-P-TOLYL DISULPHIDE IN ANEMIA OF DOGS. DOG NO. 42.

Date.	Treatment, gm.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c., thousands.	Reticulocytes, per cent.	Hematocrit, per cent.	Weight, kilos.
Oct. 18	0.5*	87	6.58	14.5	0.2	53	15.4
20	0.5	78	6.04	10.2	0.0	51	
21	0.5	70	6.10	16.9	0.6	44	
22	0.5	46	4.35	19.8	0.4	37	
23	0.5	34	3.35	21.2	0.1	30	14.7
24	0.5	24	1.83	23.9	1.2	18	
25	...†	18	2.03	39.5	10.6	16	
26	...	14	1.43	52.0	15.0	10‡ 6°	
27	...	12	0.94	59.4	26.1	15	
28	...	15	1.31	34.6	20.5	17	
29	...	23	1.49	20.9	23.5	19	14.0
Nov. 1	...	39	2.37	8.7	7.7	27	14.2
6	...	50	3.80	9.4	2.5	35	14.2
10	...	57	5.04	8.1	0.6	40	
12	0.5*	56	4.82	13.3	0.3	39	
20	0.5	42	3.87	22.2	6.0	32	15.6
24	0.5	27	2.36	20.8	16.2	26	
25	0.5	25	2.87	37.8	21.1	25	
26	0.5	24	2.38	24.8	20.2	23	
28	0.5	19	1.84	11.8	16.0	22	

* Administration of the drug commenced following the blood examination.
† Feeding discontinued.
‡ Red cells.
° White cells.

The action of di-p-tolyl disulphide upon the blood elements was in general the same as that of the n-propyl disulphide, except that it is more toxic and is apt to affect the liver, causing focal necrosis.

The n-propyl disulphide possesses an extremely strong unpleasant odor of allyl propyl disulphide and the di-p-tolyl disulphide is hepatotocic.* To overcome these difficulties benzyl disulphide, an isomer to di-p-tolyl disulphide and less toxic, odorless and a crystalline substance, was studied upon one adult dog. The results, as noted from Table III, were entirely negative. It possessed no hemolytic action when fed 1 gm. daily for eleven days. A subsequent feeding of the same dog with n-propyl disulphide was followed with a severe anemia.

TABLE III.—AN EFFECT OF BENZYL DISULPHIDE IN ANEMIA OF DOGS.
Dog No. 47.

Date.	Treatment, gm.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c., thousands.	Reticulocytes, per cent.	Hematocrit, per cent.	Weight, kilos.
Nov. 14	1*	83	7.44	4.2	0.0	50.9	13.4
20	1	76	7.04	5.8	0.0	46.9	
24	1	79	6.92	9.2	0.0	48.5	
25†	1	81	7.56	5.2	0.0	50.0	
26‡	1*	79	7.16	14.4	0.0	51.3	13.4
26							
29	...	60	5.84	19.8	0.3	38.2	13.0
Dec. 1	...	31	2.33	26.3	4.5	21.7	

* Feeding commenced after the blood examination.
† The last feeding of benzyl disulphide.
‡ Placed on 1 cc. of n-propyl disulphide daily.

L-cystine, in 1-gm. daily doses, given to two dogs for eight and fourteen consecutive days respectively was followed by only mild and indefinite changes in the blood constituents. Even these results are questionable because we were not certain that these dogs were entirely free from respiratory infections, though both dogs responded similarly (Table IV).

TABLE IV.—AN EFFECT OF FEEDING L-CYSTINE TO DOGS.
Dog No. 44.

Date.	Treatment, gm.	Hb. (Sahli), per cent.	R. b. c., millions.	W. b. c., thousands.	Reticulocytes, per cent.	Hematocrit, per cent.	Weight, kilos.
Oct. 16	1*	90	8.02	9.8	0.0	56	8.5
20	1	80	7.92	14.1	...	50	
21	1	77	7.74	16.1	0.0	48	
22	1	81	8.06	16.6	1.5	47	
23	1	78	7.54	20.0	0.4	48	8.3
25	1	81	6.88	18.3	0.2	48	
27	1	76	6.70	12.7	0.0	45	
29†	1	79	6.68	6.4	0.0	46	8.2

* Feeding commenced after the blood examination.
† The last feeding of l-cystine.

* Histopathologic changes induced by feeding of the disulphide compounds will be reported in another paper.

Summary. The n-propyl disulphide, which chemically is closely related to allyl disulphide and the di-p-tolyl disulphide, causes severe anemia in dogs through a hemolytic action upon the red cells. The rapid hemolysis of the red cells is followed with a high degree of leukocytosis and marked signs of red cell regeneration, as evidenced by a large number of reticulocytes and normoblasts thrown in the circulating blood when the hemoglobin falls below 30 per cent and the red cells decrease below 3,000,000 per c.mm. The benzyl disulphide, although isomeric with the di-p-tolyl disulphide, lacks entirely the hemolytic action of the latter. This may be due to the fact that the benzyl disulphide is decomposed in the intestinal tract before it can enter the circulating blood stream, or it may be due to its oxidation after absorption, the latter reaction being typical of benzyl compounds. The lack of strong action of l-cystine when given by mouth, is probably due to its decomposition in the intestinal tract.

The hemolytic action of the n-propyl disulphide and the di-p-tolyl disulphide appears to be similar to that of phenylhydrazine,[3] though the chemical nature of the substance is unlike.

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EFFECTS OF OVERDOSES OF GERMANIUM DIOXID UPON THE BLOOD AND TISSUES OF RABBITS.

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Through the work of Muller and associates[1] in recent years on the effects of Germanium dioxid upon the blood and bone marrow of animals my attention was attracted to this substance that, as was claimed, was able to act as an oxygen carrier in the blood and as a stimulant to the bone marrow. It is obvious that a substance possessing such qualities in the presence of a low toxicity might prove valuable in the fight against cancer. The additional load of oxygen carried by GeO_2 in the blood and released in the tissue might act as a kind of oxygen therapy recommended by Fischer-Wasels[2] as a treatment for malignant tumors and the stimulating effect on

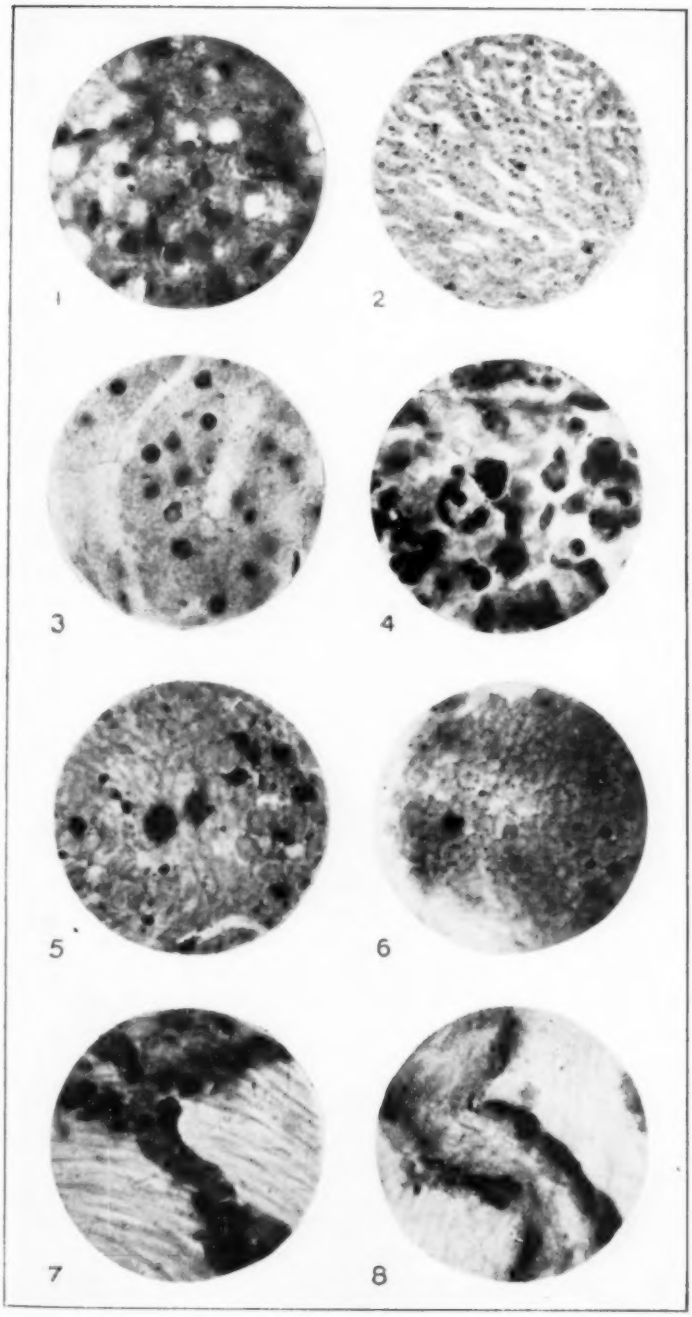

FIG. 1.—Fine granular deposits in liver cells.
FIG. 2.—Coarse granular precipitations in the liver with necrosis.
FIG. 3.—Fine granular pigment in renal tubules.
FIG. 4.—Spleen with phagocytes filled with brown deposits.
FIG. 5.—Interalveolar septum of lung with coarse dark brown deposits in the alveolar epithelium.
FIG. 6.—Vascular wall of venous plexus with brown pigmentation in the endothelial cells.
FIG. 7.—Leukocytes of a hemorrhagic exudate in bronchopneumonia filled with coarse blackish granules.
FIG. 8.—Delicate brown network in the blood of a venous plexus of the bladder.

the activities of the bone marrow would represent a valuable agent against the anemia so frequently observed in these conditions. Considering also its possible effect upon the reduction-oxidation process of the cells, a careful and thorough investigation of the physiologic and pathologic effects caused by this substance seemed to be indicated in the interest of cancer research.

It was thought advisable before any work in direct application of these findings and considerations on the cancer problem was to be attempted to repeat and elaborate some of the investigations of Muller in regard to the changes occurring in the blood and to extend them by tissue examinations of the animals treated. The results of this study are reported in this communication.

A total of 15 rabbits was used in the experiments, 10 of them were injected with colloidal Germanium dioxid and 5 served as controls during the various phases of the work. The author had moreover the opportunity to examine the organs of 6 guinea-pigs used in experiments of Dr. Muller on the toxicity of Germanium dioxid preparations. The weight of the rabbits used varied from 2500 to 3300 gm. at the start. It was attempted to introduce the Germanium dioxid in an isotonic colloidal solution containing 0.02 gm. per 100 cc. and neutralized by the addition of 1 per cent NaOH by the intravenous route. But as the animals showed the signs of a marked shock this method was abandoned and the subcutaneous injection into the tissue was substituted.

Effect of Colloidal GeO_2 Upon the Weight. The animals were first injected with a solution containing 0.02 gm. of GeO_2 per 100 cc. and later with a solution containing 0.04 gm. per 100 cc. The amounts and intervals of the medication and the weights observed are listed on Table I. When the final weights were taken the animal was either dead or it was in a dying condition. The table illustrates well the claim made by Muller that the colloidal GeO_2 solution, as he used it, produces a marked drop in weight. While our findings substantiate this statement of Muller, they show moreover that this effect occurs only, if rather large doses are given. There were only minor variations in weight remaining in physiologic limits as long as the dose used was rather small. The losses in weight sustained by the different animals during the experiment are as follows: Animal No. 1 lost 15 per cent; No. 2, 13 per cent; No. 3, 10 per cent; No. 4, 27 per cent; No. 8, 21 per cent; No. 9, 20 per cent; No. 10, 15 per cent, and No. 11, 10 per cent. It may be mentioned that the animal with the most marked drop in weight (No. 6 with 27 per cent) was in a dying state when the weight was taken. It was killed immediately afterward with ether. The resistance of the individual animal against the toxic doses of colloidal GeO_2 varies apparently considerably, if the loss in weight can be regarded as an index in this respect.

TABLE I.—WEIGHTS OF RABBITS TREATED WITH COLLOIDAL GeO_2.

Date. 1930.	GeO_2.	Animal weights in grams. No. 1.	No. 2.	No. 3.	No. 4.
June 26	10 cc. 0.02%	3299	2785	2844	2811
June 27	...	3260	2730	2910	2765
June 28	10 cc. 0.02%	3165	2695	2790	2740
June 29	...	3230	2760	2835	2630
June 30	10 cc. 0.02%	3180	2760	2880	2590
July 1	...	3195	2700	2865	2605
July 2	10 cc. 0.02%	3185	2775	3000	2605
July 3	...	3120	2665	2985	2485
July 4	10 cc. 0.04%	3135	2730	2955	2590
July 5	...	3060	2575	2860	2425
July 6	...	3245	2730	3030	2455
July 7	20 cc. 0.04%	3180	2790	2940	2455
July 8	...	3030	2665	2865	2275
July 9	20 cc. 0.04%	3090	2750	2790	2150
July 10	...	2970	2635	2730	2075+
July 11	20 cc. 0.04%	2925	2590	2590	
July 12	...	2835	2560	2560+	
July 14	...	2805+	2440+		
		No. 8.	No. 9.	No. 10.	No. 11.
July 30	20 cc. 0.04%	2695	2605	2880	2395
July 31	20 cc. 0.04%	2680	2545	2776	2275
Aug. 1	...	2545	2380	2680	2150
Aug. 2	15 cc. 0.04%	2455	2455	2695	2240+
Aug. 4	...	2120+	2275	2240+	
Aug. 5	...	...	2150		
Aug. 6	...	...	2075+		

In consideration of the fact that 1 per cent NaOH was used to enable the solution of the powdered GeO_2 it was deemed advisable to study the effect of each of these two substances upon the weight curve. Animal No. 14 was first injected with a dense suspension of powdered GeO_2 into the subcutaneous connective-tissue. When the effect of this medication became apparent the animal received four days after the first injection daily intravenous injections of increasing amounts of a suspension of GeO_2 in normal saline containing 0.02 gm. GeO_2 per 100 cc. Animals No. 15 and 16 received daily subcutaneous injections of a 1 per cent NaOH solution in normal saline. The results obtained are noted on Table II. The results of these experiments seem to indicate that the drop in weight seen in the animals injected with the colloidal GeO_2 solution is not due to the combined action of the GeO_2 and of the NaOH present in the solution upon the organism, as NaOH solution alone in the proportional amounts is not able to reduce the weight. The loss in weight of rabbit No. 15 was caused by necroses and infections in the subcutaneous tissue following the injection of the NaOH solution.

Effects of Colloidal GeO_2 Upon the Blood. Germanium dioxid medication produces doubtlessly marked fluctuations in the number of erythrocytes of the peripheral blood (venous), as that is evident from the figures listed on Table III. The blood was taken from the ear veins of the rabbits. There are two changes which are uni-

formly observed in all animals. After several fluctuations above and below the original level, the number of erythrocytes reaches in all animals a more or less low figure after the fifth injection and shows a considerable rise during the preagonal stage.

TABLE II.—WEIGHTS OF RABBITS TREATED WITH A GeO_2 SUSPENSION AND 1 PER CENT NaOH SOLUTION.

(*a*) Rabbit No. 14 injected with GeO_2 suspension.

Date, 1930.	GeO_2.	Weight, gm.
Oct. 10	5 cc. dense suspension subcutaneously	2650
Oct. 13	1 cc. 0.02% intravenously	2550
Oct. 14	1 cc. 0.02% intravenously	2550
Oct. 15	4 cc. 0.02% intravenously	2500
Oct. 16	15 cc. 0.02% intravenously	2565
Oct. 17	27 cc. 0.02% intravenously	2565+

(*b*) Rabbits No. 15 and No. 16 injected with 1 per cent NaOH solution.

Date, 1930.	1% NaOH.	Weight, gm.	
		No. 15.	No. 16.
Oct. 13	20 cc. subcutaneously	2525	2380
Oct. 14	20 cc. subcutaneously	2550	2350
Oct. 15	20 cc. subcutaneously	2500	2470
Oct. 16	20 cc. subcutaneously	2550	2365
Oct. 17	20 cc. subcutaneously	2575	2500
Oct. 18	.....	2525	2500
Oct. 19	40 cc. subcutaneously	2500	2515
Oct. 20	40 cc. subcutaneously	2465	
Oct. 21	40 cc. subcutaneously	2510	
Oct. 22	40 cc. subcutaneously	2470	
Oct. 23	40 cc. subcutaneously	2450	
Oct. 24	40 cc. subcutaneously	2430	
Oct. 25	40 cc. subcutaneously	2360	
Oct. 26	.....	2300	
Oct. 27	.....	2300	
Oct. 28	.....	2225	
Oct. 29	.....	2325	
Oct. 30	.....	2300	
Oct. 31	.....	2375	

There is in general an increase in the number of leukocytes present, especially during the final stage of the experiment. Similar variations are observed in the lymphocytic-leukocytic ratio. The number of neutrophilic leukocytes increases with the final leukocytosis.

In none of the numerous blood smears examined was evidence of an increased production or regeneration of erythrocytes noticed. There were no nucleated red blood corpuscles, no poikilocytosis, no anisocytosis, no chromatophilia present.

The fragility test was essentially negative, with perhaps the exception of the last two examinations made of animal No. 6, where an increased fragility was found.

Effects Upon the Sugar Content and the pH of the Blood. The animals were starved for fifteen hours. The blood for the first two examinations was obtained from the ear veins, while the blood of the subsequent tests was taken from the heart by puncture. The

TABLE III.—BLOOD FINDINGS IN RABBITS TREATED WITH COLLOIDAL GeO_2.

Date.	GeO_2.	Effect upon the blood.												Differential count.																				Fragility test. NaCl, per cent.			
		Hemoglobin (Sahli), per cent.				Erythrocytes (millions).				Leukocytes (thousands).				1.					2.				4.				6.											
		1.	2.	4.	6.	1.	2.	4.	6.	1.	2.	4.	6.	L.	M.	Nl.	El.	Bl.	L.	M.	Nl.	El.	Bl.	L.	M.	Nl.	El.	Bl.	L.	M.	Nl.	El.	Bl.	1.	2.	4.	6.
June 24	10 cc. 0.02%	90	75	80	83	7.48	6.75	7.25	7.04	9.6	5.4	8.1	14.4	67	..	33	..	..	73	7	20	..	..	54	2	43	..	..	65	..	35	..	..	0.46 0.34	0.46 0.36	0.46 0.38	0.48 0.36
June 28	10 cc. 0.02%	75	78	84	80	8.36	8.07	7.50	8.80	12.0	6.6	13.5	14.0	57	..	31	9	3	88	..	10	1	1	77	2	21	..	..	87	5	7	..	1	0.50 0.40	0.48 0.34	0.52 0.40	0.48 0.36
June 30	10 cc. 0.02%	70	70	75	78	7.50	8.12	8.22	6.86	12.8	10.3	11.9	8.3	71	1	21	7	1	83	5	11	1	..	65	..	35	..	..	61	1	38	..	..	0.46 0.38	0.48 0.38	0.48 0.40	0.48 0.34
July 2	10 cc. 0.02%	72	69	73	77	7.25	7.86	7.14	7.37	10.0	9.3	19.8	11.3	78	1	16	5	..	76	1	22	1	..	63	..	37	..	..	50	5	39	3	3	0.48 0.34			
July 4	10 cc. 0.04%	78	66	65	81	9.48	7.26	5.96	8.60	17.0	9.7	16.0	13.1	77	1	19	3	..	78	1	32	..	..	53	..	47	..	..	50	2	47	1					
July 7	20 cc. 0.04%	67	70	60	68	6.97	5.21	4.08	4.06	18.0	7.2	12.4	14.1	57	1	40	2	..	80	1	19	..	..	70	..	30	..	..	84	2	14						
July 9	20 cc. 0.04%	65	70	64	60	7.30	6.50	6.10	8.54	12.2	8.6	15.8	14.2	94	..	5	1	..	69	..	30	..	1	75	2	23	..	..	53	..	47	..	..	0.46 0.36	..	..	0.52 0.42
July 11	20cc. 0.04% No. 2	67	66	69	73	7.20	6.28	8.45	10.78	14.4	12.6	17.2	18.4	59	..	37	4	..	62	2	36	..	..	43	..	57	..	..	33	..	67	..	..	..	..	..	0.52 0.38
July 12	....	75	..	..	..	8.51	..	..	..	22.2	19.2			33	2	73	2	..	18	..	82																
July 14	....	..	80	..	..	..	10.28																														

L., lymphocytes; M., monocytes; Nl., neutrophilic leukocytes; El., eosinophilic leukocytes; Bl., basophilic leukocytes.

Hagedorn-Jensen method was used for the determination of the blood sugar and the Hastings-Sendroy bicolor standard method for the determination of the pH, with such improvements in the technique as devised in our laboratories.[3]

TABLE IV.—BLOOD CHEMISTRY FINDINGS IN RABBITS TREATED WITH COLLOIDAL GeO_2.

Date, 1930.	GeO_2	Blood sugar, mg.			pH.		
		No. 8.	No. 9.	No. 10.	No. 8.	No. 9.	No. 10.
July 30* . .	20 cc. 0.04%	93	96	104	7.27	7.38	7.24
Aug. 1 . .	20 cc. 0.04%	..	97	117	7.32	7.38	7.32
Aug. 4 . .	20 cc. 0.04%	93	85	99	7.35	7.22	7.33
Aug. 6 . .	...	..	117	..	..	7.44	

* Injections given directly after blood was taken.

The variations of the blood sugar level during the experimental period are too irregular to enable any definite conclusions in regard to the possible effects of GeO_2 on the sugar metabolism. The figures obtained at the pH determinations seem however to indicate that GeO_2 medication produces a tendency toward alkalosis, if large toxic doses are employed.

General Symptomatic Effects of GeO_2 Medication. There were no changes from the normal behavior while the animals received relatively small doses of colloidal GeO_2 (10 cc., 0.02 per cent). With the onset of the injection of large doses (20 cc., 0.04 per cent) definite clinical effects could be observed. The animals became listless, weak and were lying in their cages most of the time. The appetite decreased considerably for the dry food (oats), but remained rather good for the green food (lettuce). The bowel movements became first soft and later liquid and were apparently increased in frequency as the animals were always wet during the last days of the experimental period. The respiratory rate remained normal, also the temperature, which was rectally taken five times daily. The blood pressure decreased evidently considerably, as it became during the last days almost impossible to withdraw any blood from the ear veins. Compression of the veins by pressure of the finger showed a very slow filling of the vessels when pressure was released. The blood was brownish red, thick and was leaving sluggishly the more or less collapsed veins of the ear.

AUTOPSY FINDINGS. The microscopic examination of the organs showed a marked hyperemia of the internal organs and a marked decrease of the amount of fat tissue. The fecal material in the large intestine was usually of a soft or liquid consistency. On the cut surface of the liver of rabbit No. 4 irregular grayish-white areas were noticed which represented apparently thickenings of the interstitial connective tissue. The examination of the urine obtained by puncture of the bladder was in general negative for albumin, sugar and sediment, with the exceptions of the findings in one of the animals which had received daily injections of 20 cc. of 0.04 per cent GeO_2, where albumin and numerous granular casts and fatty degen-

erated round epithelial cells were found. Similar urinary findings were obtained by an examination of the urine of rabbit No. 14, injected with the suspension of GeO_2.

MICROSCOPIC FINDINGS. *Brain.* The brain tissue is somewhat edematous and the vessels are hyperemic. Small perivascular accumulations of phagocytic cells are present in the cortex of animal No. 2. The meninges are hyperemic.

Submaxillary Gland. The vessels are hyperemic.

Thyroid Gland. Hyperemic vessels.

Lung. The vessels of the lungs are hyperemic. Hemorrhages into the alveoli are not infrequently seen. Smaller foci of leukocytic infiltrations in the alveolar walls and exudation into the alveolar space are occasionally observed beside a serous exudate in adjacent alveoli.

Heart. The muscular tissue is in general normal. Only in animal No. 2 a vacuolar degeneration of the muscle is noticed.

Stomach. The mucosa of the stomach is hyperemic.

Intestine. The mucosa is somewhat infiltrated with lymphocytes and leukocytes, especially in the large bowel. The vessels are hyperemic. A brownish to greenish-brown amorphous material is found in the subepithelial connective tissue in some guinea pigs injected intraperitoneally with crystalline GeO_2.

Liver. The liver is edematous and the vessels are hyperemic. There are occasional small focal necroses observed, and in one instance a larger necrosis of infarct character is seen. The Kupffer cells are always found more or less loaded with these brown deposits. Usually the brown-reflecting crystalline material is found either in large clumps or in fine granules also in the liver cells and phagocytic cells of the interstitial connective tissue or it appears like a fine granular dustlike substance in the liver cells. An interstitial fibrosis is seen in the liver of rabbit No. 4 of apparently long standing. In only two livers (No. 2 and No. 6) small amounts of glycogen can be demonstrated with special staining.

Spleen. The sinuses are filled with erythrocytes and desquamated sinus endothelial cells containing more or less large amounts of brown deposits of amorphous and crystalline character. These are also found in leukocytes and large phagocytic cells of the spleen. Special staining for iron shows that some of these deposits are iron positive and many are iron negative. In a few instances a blue granule is found in a dark-brown mass.

Pancreas. There are no pathologic changes with exception of hyperemia.

Adrenal Gland. The vascular system of this organ is more or less markedly hyperemic, especially in its medullary portion where sinusoid formations are sometimes observed.

Kidney. There is a moderate to marked hyperemia present. The capillaries of the glomeruli are distended with blood. The epithelium of the tubular lining contain the fine granular brown deposits. The tubular epithelium shows them mainly at the base of these cells. Degenerative changes of these cellular elements are not infrequent and of a moderate to marked degree.

Urinary Bladder. Normal.

Testis and Epididymus. The spermatogenesis is good. The ducts of the epididymis are filled with spermatozoa.

Ovary and Tube. Normal.

Femur. Except for a moderate degree of hyperemia there is no deviation of the myeloid tissue from the normal appearance. The erythrocytes have in some of the specimens a somewhat brownish tint.

The bone marrow consists of a mixture of fat marrow and myeloid marrow. The latter predominates in the distal portions of the shaft. It is mainly composed of round marrow cells with round dark-stained nuclei.

Giant cells are occasionally seen. The number of immature erythrocytes is about the same as that seen in the bone marrow of untreated animals. Individual variations occur.

Tissue cultures of bone marrow of chick embryos, to the culture medium of which small amounts of colloidal GeO_2 were added, did not show any stimulating effect of the GeO_2 upon the proliferative activity of the bone-marrow cells. The culture medium consisted of equal parts of chicken plasma and a solution of 1 cc. of 0.02 gm. GeO_2 in 100 cc. of Tyrode solution.

Ear. The subcutaneous tissue of an ear in which an intravenous injection of GeO_2 was attempted shows large masses of a brownish pigment in the tissue and tissue cells.

Comment. The results of these experiments agree to a certain extent with those of Muller and associates, as loss of weight and temporary increases of the number of erythrocytes could be recorded. But it was found difficult and partly impossible to accept Muller's conceptions in regard to the causative mechanism of these changes without restriction and modification.

While Muller was first inclined to believe that the drop in weight is mainly due to increased oxidative processes in the body caused by the oxygen given off by the GeO_2 in the tissues, I feel rather certain on the basis of my own findings and observations that increased tissue oxidation plays only a minor rôle in this phenomenon because there is no decrease in the respiratory rate, no increase in temperature, no decrease of blood sugar, no increase in blood pressure, no drop in number of erythrocytes and hemoglobin present. All or at least several of these symptoms may justly be expected to be evident, before increased oxidation of the tissue may be accepted as the main causative factor for the rapid and marked decrease in weight in some of these animals. Moreover one has to consider that the depressing effect of GeO_2 on the circulation is apt to compensate at least for some of the oxygen carrying power of GeO_2, a quality, in support of which Muller has brought forward important chemical evidence. It seems to me by far more probable that dehydration has to be regarded as the main factor for this phenomenon, as the most marked drops in weight were observed in the presence of a concomitant diarrhea. Moreover the considerable fluctuations in the number of erythrocytes point to marked changes in the water content of the blood. Especially the observation of a rather dark red to reddish brown blood in some of the animals just before death can be taken as definite evidence of marked loss of water from the organism. Germanium acts upon the colon apparently in a similar fashion as arsenic, producing also a colitis, which may resemble in some respects those intestinal disturbances seen in cholera where also marked and rapid loss of weight and increase of erythrocytes are found as sequelæ of dehydration.

There exist also considerable difficulties to bring sufficient proof in support of a stimulative effect of Germanium on the bone marrow and especially its erythropoietic part, because the temporary fluc-

tuations in the number of erythrocytes are more likely to be interpreted as evidence of changes in the water content of the blood as indicated above. Sudden and marked increases of erythrocytes by stimulation of the bone marrow would be characterized by the appearance of immature forms of the cells in the peripheral blood (nucleated red cells, polychromatophilic cells, etc.). But they were absent in all of the numerous smears examined. Moreover the histologic examination of the bone marrow did not show any deviation from the normal picture (Kesser[5]). It is also a well established fact that not excess of oxygen, but an insufficient oxygenation of the blood acts as a stimulus upon the erythropoietic system, as a symptomatic polycythemia is seen in persons with congenital heart lesions and those exposed to the mountain air with its low oxygen content. According to Harrop, Elmer and Schaub[4] a disturbed diffusion of oxygen in the lungs causes a lowered oxygen tension in the tissues (bone marrow) resulting in an increased formation of erythrocytes.

The leukocytosis observed in the treated animals is regarded as due to changes in the concentration of blood and due to distributory changes similar to those seen after parenteral injections of colloidal metals, proteins, and so forth. Inflammatory processes in the lung, bronchopneumonia, may have contributed during the later stages of the experimental period to the increase in the number of these cells.

The determination of the exact chemical nature of the brown precipitations found in the spleen, liver and kidney made considerable difficulties. It was however established that they do not represent formalin deposits as they were seen in tissues which did not come in contact with formalin, but were fixed in alcohol. They are also not precipitations of the stains used as they could be demonstrated in sections of fresh and fixed unstained tissue. In tests for their possible hematogenous origin the pigmentations showed a rather peculiar, inconsistent reaction with Mallory's iron stain. It occurred that the brown granulations were sometimes iron positive and sometimes iron negative. This discrepancy was not only seen in organs of different animals, but in organs of the same animal. It was found that the pigmentations in the spleen could be iron positive, while the brown deposits of the liver proved to be predominantly iron negative and *vice versa*, in spite of the fact, that the sections of both organs were stained simultaneously with the same stain and same technique, In the liver of rabbit No. 14, which was injected with the GeO_2 suspension larger, white, reflecting, crystalline plates were seen mainly in the subcapsular region. These deposits showed upon iron staining often a bluish tinted periphery, although there can be no doubt that they represent larger crystals of the injected GeO_2. It was furthermore noticed that even the bluish colored pigments become colorless and disappear, if treated with a mixture of ammonia water (diluted 1 to 15) and 3 per cent

hydrogen peroxid, equal parts, while the iron containing pigments and lipofuscin deposits in sections of hemosiderosis and hemochromatosis remained yellow or brown, if treated with this reagent. As it is known that Germanium compounds are dissolved by a reagent of the above constitution it appears probable that the brown pigments observed may contain a lower oxidation product of Germanium possibly bound or attached to a derivative of hemoglobin in some instances, apparently indicated by the positive iron reaction. Such a combination between a Germanium compound and a hematogenous pigment, if existing, may find its parallel in a similar product in which GeO_2 is apparently bound in some way to the hemoglobin of the erythrocytes of the venous blood as Muller could show. Another factor in support of the conception of the Germanium nature of the brown deposits may be seen in the fact that they are rather scantily found in the organs of those animals which died or were killed several days after receiving their last injection of colloidal GeO_2. This observation is very well in accordance with the findings of Muller who notes that any excess of GeO_2 injected is eliminated to its greater part during the first forty-eight hours after introduction. It may be therefore justly assumed that any precipitations formed in the organs of these animals were mobilized and the dissolved substances excreted with the urine during the period which elapsed between the last injection and the death of the animals.

Besides these fine brown granular intracellular deposits which are doubtlessly products of the medication there occurred very frequently in the formalin fixed material very extensive, usually more blackish brown and coarser precipitations only exceptionally and scantily seen in the alcohol fixed tissue. These deposits were remarkable on account of their affinity to certain types of cells and of their peculiar arrangement and location in the blood. They were mainly found in the reticulo-endothelial cells (Kupffer cells of liver and phagocytic cells of the spleen and lung), endothelial cells of vessels (especially venous plexus) and in the leukocytes of the blood or hemorrhagic exudates. In addition to this mainly intracellular occurrence in the organs slender brown reflecting needles were seen in the blood. In other instances the erythrocytes appeared to be surrounded by a delicate, granular, brown membrane. While there exists the possibility that these deposits represent intra vitam precipitations of metallic Germanium or of its low oxidation products or condensation products of Germanoformic acid with proteins, it seems to be more probable that they are formalin precipitations, as deposits identical in color, appearance, location and arrangement may be observed in ordinary tissue fixed with formalin. The just mentioned qualities of the deposits point, however, to the existence of specific affinities between organic substances and the reactive exogenous agent whatever its nature may be.

Conclusions. 1. The loss of weight in animals treated with toxic doses of Germanium dioxid in colloidal solution is apparently mainly due to dehydration and caused to a lesser extent by an increase in the oxidative processes of the organism.

2. Temporary increases in the number of erythrocytes following administrations of colloidal GeO_2 are best explained by fluctuations in the water content of the blood. A stimulative effect of this substance on the erythropoietic system seems to be improbable on the basis of the evidence available.

3. Toxic doses of colloidal GeO_2 cause a marked drop in blood pressure.

4. Excessive amounts of colloidal GeO_2 injected result in the production of massive brown precipitations in various organs.

5. On account of the oxygen carrying power of GeO_2 an investigation into its possible anticancerous qualities seems to be indicated.

My thanks are due to Prof. Dr. J. H. Muller, Department of Chemistry, University of Pennsylvania, for the preparation of the Germanium dioxid solution used and the kind interest he showed in the chemical aspects of this work. I am furthermore indebted to Miss M. Russell for technical assistance during the experiments and Miss G. Woodward and Miss J. Schoonover for the chemical analyses of the blood.

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STUDIES ON THE "ACID DEFICIT" IN PERNICIOUS ANEMIA.

WITH REPORT OF A CASE SHOWING RETURN OF FREE ACID.

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Many investigators prior to the introduction of liver in the treatment of pernicious anemia demonstrated the almost constant occurrence of achlorhydria in this disease. On this point Cornell,[1]

in a review of the etiology of pernicious anemia, may be quoted as follows: "If one fact has received ample confirmation in connection with the entire subject of pernicious anemia, it is this, the stomach contents do not contain free hydrochloric acid."

In a search of the literature we have found references to 2 patients suffering with pernicious anemia who showed a return of free hydrochloric acid in the gastric contents. Shaw's[2] patient showed a return of free hydrochloric acid following a spontaneous remission, while Heeres'[3] patient showed a return of free hydrochloric acid following liver therapy. We wish to report a third case.

Case Report. J. Y., male, white, aged sixty-nine years, nativity, United States, laborer, was admitted on February 14, 1929, in first relapse. No history of bleeding or of previous liver therapy.

Chief complaints: Progressive general weakness, dyspnea, palpitation, sore tongue, loss of appetite with distaste for meat, alternating diarrhea and constipation, numbness and tingling in fingers and toes, especially the latter, girdle sensation and pallor of skin.

Neurologic examination showed moderately severe subacute combined system disease with predominant involvement of the posterior columns.

Laboratory data: Hemoglobin, 47 per cent; red cell count, 1,300,000; color index, 1.8; white cell count, 1900; plates not numerous. Differential count: Myelocytes, 0; metamyelocytes I, 0; metamyelocytes II, 0; polymorphonuclears, 34 per cent; lymphocytes, 57 per cent; monocytes, 7 per cent; eosinophils, 2 per cent; basophils, 0; plasma cells, 0.

Red cells in stained film showed marked changes in shape and size, with a predominance of oval macrocytes. Polychromatophilia was seen only occasionally. In general, the red cells were deeply and uniformly stained. Resistance of the red cells to hypotonic salt solution, on admission: Patient: Beginning hemolysis, 0.43 per cent sodium chlorid; complete hemolysis, 0.36 per cent sodium chlorid. Control: Beginning hemolysis, 0.44 per cent sodium chlorid; complete hemolysis, 0.32 per cent sodium chlorid. On discharge: Patient: Beginning hemolysis, 0.46 per cent sodium chlorid; complete hemolysis, 0.28 per cent sodium chlorid. Control: Beginning hemolysis, 0.46 per cent sodium chlorid; complete hemolysis, 0.33 per cent sodium chlorid.

Direct van den Bergh was negative; the indirect was positive and quantitatively showed a slight increase. The urinary urobilinogen was not increased. The stool examination was negative for pus, red cells, excess mucus, ova, parasites and Charcot-Leyden crystals.

The gastrointestinal film series and fluoroscopy were negative for ulcer and new growth. Prostatic, proctoscopic and sigmoidoscopic examinations showed nothing striking. The basal metabolic rate was +14. A detailed report of the gastric acidity curves is given further on.

After the diagnosis of pernicious anemia was made the patient was given a daily dose of a potent liver fraction (Marine Liver Extract—White)* A satisfactory hematologic and clinical response followed. (See Fig. 1 for reticulocyte curve.) Subsequently he was put on a daily maintenance dose. There has been no relapse to date, although stained blood films continue to show variation in the size of the red cells, especially in the direction of macrocytosis.

A fractional gastric analysis at the time of admission to the hospital revealed achlorhydria even after the injection of 0.5 mg. of histamin.

* Made by the White Laboratories, of Newark, New Jersey.

Following two months' treatment when the remission had been established a gastric analysis revealed absent free acid for the first seventy-five minutes of the test, but on the ninety-minute extraction free acid equivalent to

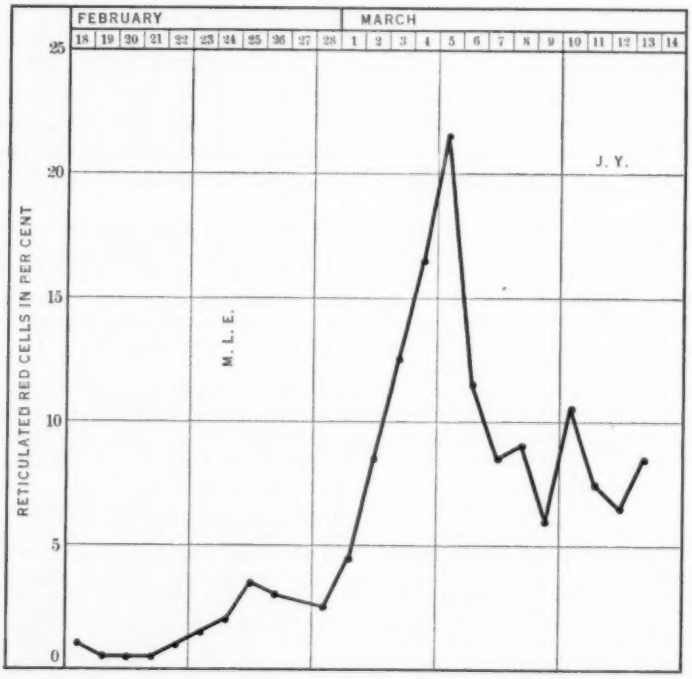

FIG. 1.—Reticulocyte response to treatment M.L.E.—Marine liver extract.

10 cc. of $\frac{N}{10}$ sodium hydroxid per 100 cc. of gastric contents was found. Reëxamination a year later showed free acid equivalent to 36 cc. of $\frac{N}{10}$ sodium hydroxid. (Table I.)

TABLE I.—GASTRIC ANALYSES IN PATIENT J. Y.

Date.		Fasting.	15 min.	30 min.	45 min.*	60 min.	75 min.	90 min.
2/16/29	T. A.†	8	10	6	6	11	20	13
	Free‡	0	0	0	0	0	0	0
3/22/29	T. A.	30	22	18	24	21	30	44
	Free	0	0	0	0	0	0	10
2/15/30	T. A.	12	2	6	14	20	40	48
	Free	−20§	−6	−6	2	9	27	36

* 0.5 mg. histamin intramuscularly immediately following extraction of this sample.

† T. A.—Total acidity.

‡ Free—Free acidity or acid deficit.

§ A minus sign (−) before a titration figure indicates acid deficit.

Johansen[5] showed that remissions induced by liver therapy were not associated with a return of free acid in the gastric contents. Keefer and Bloomfield[6] pointed out that considerable acid may be secreted by the stomach but not enough to change di-methyl-amino-azo-benzene from yellow to red. It occurred to us that possibly in pernicious anemia subjects the anacidity had lessened following liver treatment, but not sufficiently to give a reaction for free acid when tested by di-methyl-amino-azo-benzene. In order to test this possibility the following observations were made.

Method. Fourteen subjects suffering from pernicious anemia were studied on the wards of the Third (New York University) Medical Division of Bellevue Hospital. Each subject at the beginning of this observation was in an exacerbation of the disease. During the control period, while the diagnosis was being established, a fractional gastric analysis was performed. A test meal of 400 cc. of 6 per cent alcohol was used in every instance. The test meal was given immediately after the fasting contents was extracted by allowing it to enter the stomach through the Rehfuss tube by gravity. Following the removal of the forty-five-minute sample, 0.5 mg. of histmin was injected intramuscularly, which amount induced in every instance flushing of the face and a transient headache. Total acidity was determined by titrating a sample with $\frac{N}{10}$ sodium hydroxid using phenolphthalein as an indicator. The amount of acid necessary to add to the gastric contents before the test for free acid became positive was determined by titrating a sample of gastric contents with $\frac{N}{10}$ hydrochloric acid using di-methyl-amino-azo-benzene as an indicator. The amount of $\frac{N}{10}$ hydrochloric acid necessary to change this indicator from yellow to red we have called the acid deficit. The result is calculated on the basis of 100 cc. of gastric contents.

Results.—In Table II we have tabulated the results of the gastric analyses. A total of 31 analyses were performed on 14 patients. In 3 patients (12, 13 and 14) we were not able to repeat the analysis following treatment, but on the remaining 11 there are given results of analyses made over a period of one to fourteen months of treatment. In Fig. 2 is shown the composite curve obtained in the entire group of analyses. The average deficit in the fasting sample was 37 cc., which decreased to 10 at the fifteen-minute period and then progressively increased, reaching 33 cc. at the ninety-minute period, thereby approximating the acid deficit in the fasting sample. It can be noted that this is true of the individual tests and that there was no change in the slope of the curve following the injection of histamin at the forty-five-minute period.

In Fig. 3 we have compared the curves of the total acidity and acid deficit obtained before treatment with those following remission. It is noted that the two sets of curves practically coincide. The slightly greater acid deficit in the fasting sample before treatment

TABLE II.—TABULATION OF GASTRIC ACIDITIES.

Subject.	Date.		Fasting.	15 min.	30 min	45 min.*	60 min.	75 min.	90 min.
1.	9/25/29	T. A.†	26	3	3	6	8	10	8
		Free‡	−87§	−4	−12	−9	−17	−18	−18
	12/11/29	T. A.	20	1	2	4	5	10	15
		Free	−50	−12	−16	−20	−32	−38	−35
	5/10/30	T. A.	15	2	3	7	8	9	n. s.
		Free	−36	−12	−12	−20	−24	−33	n. s.
2.	6/20/29	T. A.	n. s.††	5	5	10	16	10	10
		Free	n. s.	0	0	0	0	0	0
	9/26/29	T. A.	12	1	3	3	4	6	qns.
		Free	−21	−4	−11	−10	−11	−16	−26
3.	6/20/29	T. A.	20	7	4	12	12	qns.**	10
		Free	0	0	0	0	0	0	0
	10/ 9/29	T. A.	6	2	5	5	5	n. s.	n. s.
		Free	−42	−9	−28	−42	−48	n. s.	n. s.
4.	3/20/29	T. A.	22	16	16	18	30	38	36
		Free	0	0	0	0	0	0	0
	4/19/29	T. A.	18	12	14	10	14	10	8
		Free	0	0	0	0	0	0	0
	10/10/29	T. A.	4	1	2	3	3	3	4
		Free	−12	−5	−6	−9	−12	−16	−24
	5/12/30	T. A.	12	2	2	8	12	8	qns.
		Free	−32	−6	−7	−27	−37	−25	−21
5.	10/15/29	T. A.	11	2	2	4	qns.	n. s.	n. s.
		Free	−34	−9	−12	−18	−22	n. s.	n. s.
	1/18/30	T. A.	8	2	2	4	4	4	4
		Free	−36	−14	−15	−15	−7	−16	−21
	4/ 8/30	T. A.	n. s.	1	2	2	2	2	3
		Free	n. s.	−10	−10	−10	−11	−16	−18
6.	10/30/29	T. A.	10	3	3	4	4	5	5
		Free	−55	−14	−16	−27	−28	−42	−52
	3/13/30	T. A.	12	2	4	4	6	6	10
		Free	−36	−16	−16	−19	−25	−28	−28
7.	10/31/29	T. A.	10	1	1	2	3	3	4
		Free	−34	−10	−11	−14	−16	−20	−29
	2/15/30	T. A.	5	1	2	2	3	qns.	6
		Free	−32	−8	−10	−17	−24	−37	−36
8.	7/30/28	T. A.	n. s.	8	6	4	10	n. s.	n. s.
		Free	n. s.	0	0	0	0	n. s.	n. s.
	11/ 5/29	T. A.	6	1	2	2	4	5	6
		Free	−25	−8	−10	−14	−20	−22	−28
	1/ 8/30	T. A.	8	2	4	6	8	10	10
		Free	−35	−11	−14	−16	−20	−21	−29
9.	11/23/29	T. A.	n. s.	1	1	2	2	3	4
		Free	n. s.	−11	−16	−17	−20	−35	−30
	4/14/30	T. A.	10	2	2	2	3	3	4
		Free	−31	−13	−111	−14	−27	−35	−35
10.	1/11/30	T. A.	n. s.	3	3	3	4	4	6
		Free	n. s.	−13	−8	−18	−22	−31	−18
	3/10/30	T. A.	6	4	6	6	6	n. s.	n. s.
		Free	−21	−11	−11	−19	−28	n. s.	n. s.
	4/ 2/30	T. A.	qns.	2	2	qns.	qns.	qns.	n. s.
		Free	−35	−13	−12	−12	−25	−28	n. s.
11.	3/ 1/30	T. A.	5	2	6	qns.	6	qns.	qns.
		Free	−50	−8	−10	−20	−22	−33	−50
	3/22/30	T. A.	qns.	2	4	qns.	qns.	qns.	qns.
		Free	−42	−17	−25	−27	−40	−42	−45
12.	2/21/30	T. A.	10	2	2	4	4	6	4
		Free	−50	−12	−13	−14	−28	−26	−20
13.	11/23/29	T. A.	3	1	2	2	3	6	qns.
		Free	−35	−13	−26	−26	−29	−30	−60
14.	5/ 2/30	T. A.	n. s.	2	2	2	3	6	n. s.
		Free	n. s.	−8	−12	−18	−20	−28	n. s.

* 0.5 mg. histamin intramuscularly immediately following extraction of this sample.
† T. A.—Total acidity. ‡ Free—Free acidity or acid deficit.
§ A minus sign (−) before a titration figure indicates acid deficit.
** qns.—Sample not of sufficient quantity.
†† n. s.—No sample could be obtained.

compared to that following treatment we believe to be without significance.

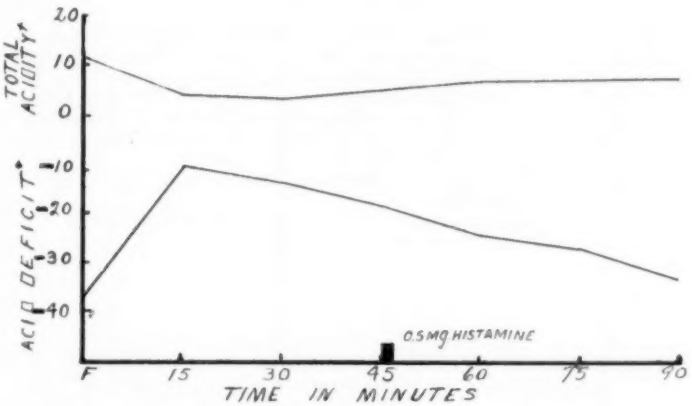

FIG. 2.—Composite gastric analysis curve of entire group.

* Acid deficit measured in cubic centimeters of tenth normal hydrochloric acid per 100 cc. of gastric contents.

† Total acidity measure in cubic centimeters of tenth normal sodium hydroxid per 100 cc. of gastric contents.

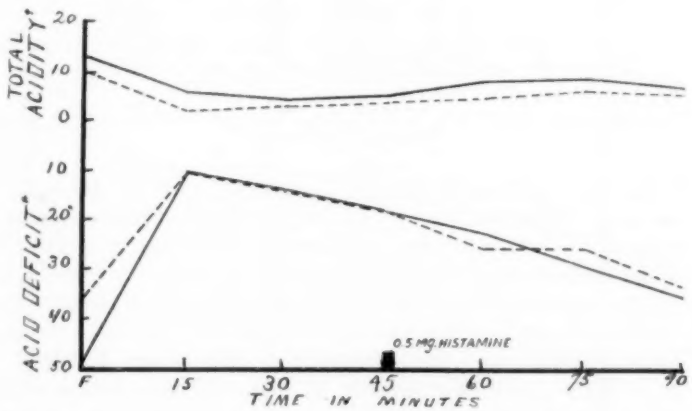

FIG. 3.—Composite gastric analysis curves before and after liver treatment.

* Acid deficit measured in cubic centimeters of tenth normal hydrochlorid acid per 100 cc. of gastric contents.

† Total acidity measured in cubic centimeters of tenth normal sodium hydroxid per 100 cc. of gastric contents.

Solid lines—before treatment.

Broken lines—after liver therapy.

Summary and Conclusions. A return of free acid in the gastric contents is reported in one patient suffering from pernicious anemia.

In 11 cases of pernicious anemia no change in "acid deficit"

could be demonstrated following liver treatment over a period of one to fourteen months.

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THE RÔLE OF CARDIAC ISCHEMIA IN PRODUCING R–T DEVIATIONS IN THE ELECTROCARDIOGRAM.*

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It has been demonstrated that the *R–T* deviations characteristic of coronary thrombosis occur also in pericardial effusion in man and in animals.[1,2] More recently evidence was presented to show that coronary occlusions can be made in normal animals without changing the *R–T* segment of the electrocardiogram, but such changes in the *R–T* segment ensue when the myocardium becomes incompetent.[3]

Three clinical cases are presented in this report to show how *R–T* deviations can be produced by myocardial ischemia in other ways besides coronary occlusion and pericardial effusion.

Case Reports. Case I.—The patient, aged fifty-eight years, entered the hospital on February 10, 1930, in an unconscious state. From the history later obtained from the patient he said that he had been in a conference and was just about to sign a contract when he experienced a peculiar sensation which was difficult to explain. This sensation made him feel as though the room was stuffy, and he got up and opened a window. He sat down and tried to smoke a cigar, but it did not taste right. He threw

* Aided by the Emil and Fannie K. Wedeles Fund, for the Study of Diseases of the Heart and Circulation, at Michael Reese Hospital.

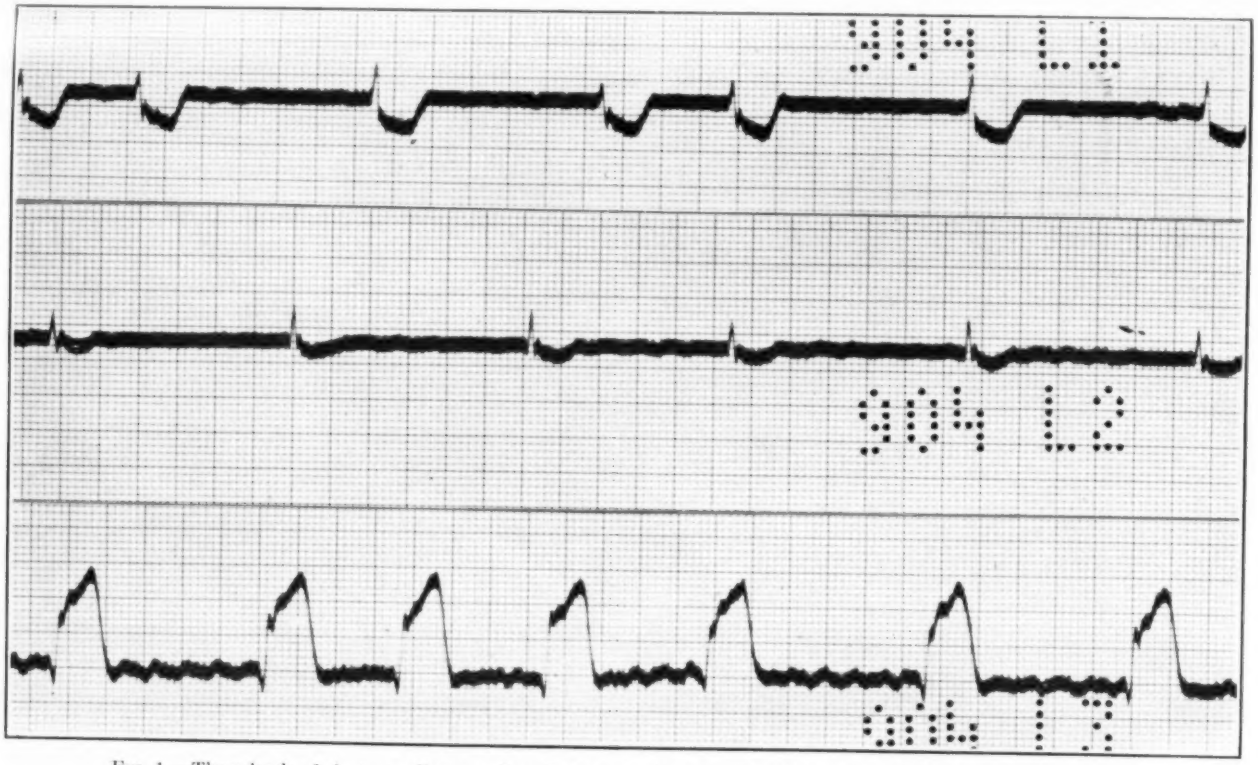

FIG. 1.—Three leads of electrocardiogram, Case I, taken on February 10, 1930, two and a half hours after attack.

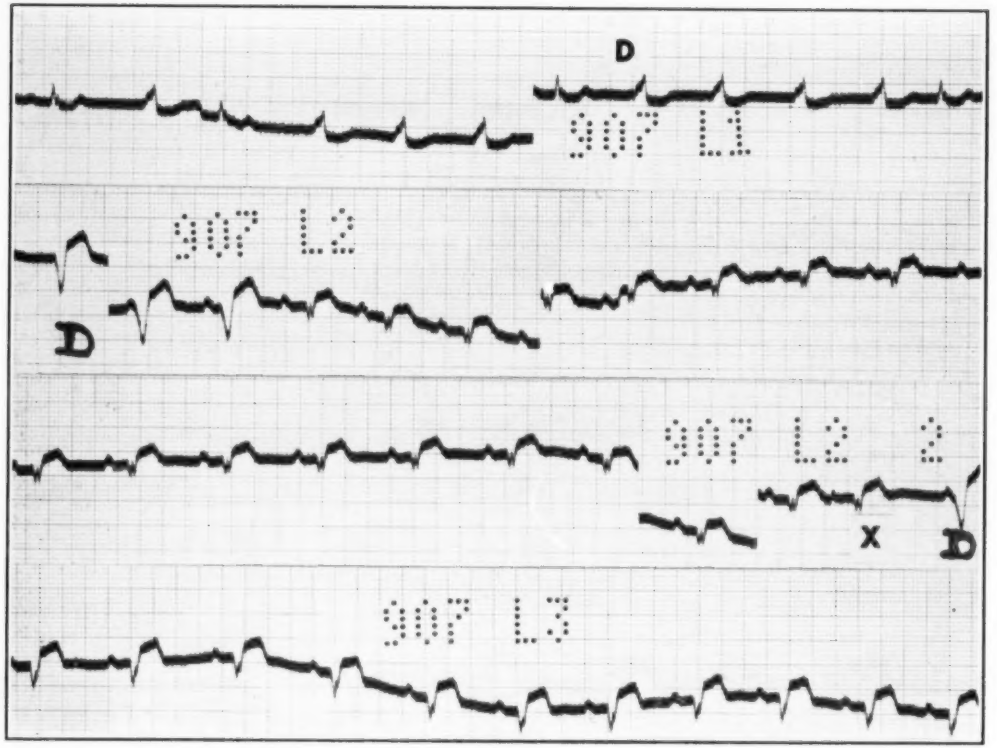

FIG. 2.—From same patient taken, February 11, 1930, fifteen hours after attack.

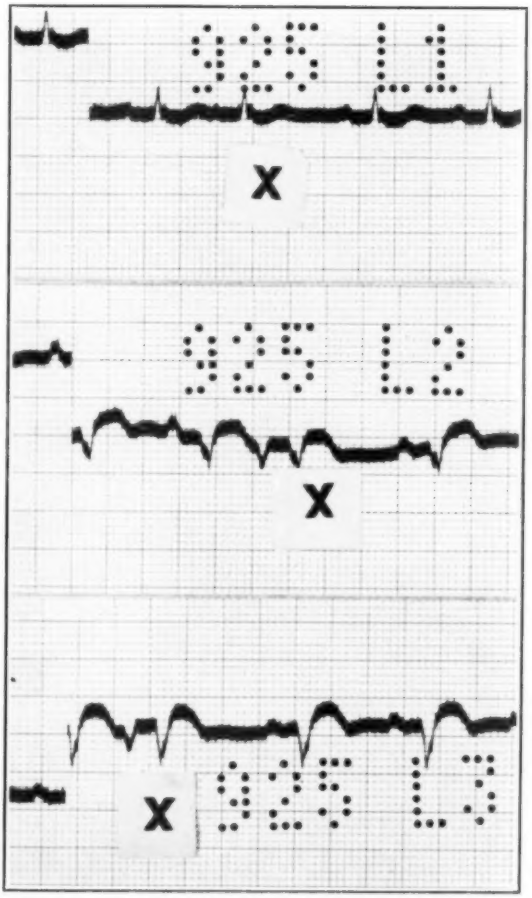

FIG. 3.—From same patient taken, February 19, 1930.

FIG. 2.—From same patient taken, February 11, 1930, fifteen hours after attack.

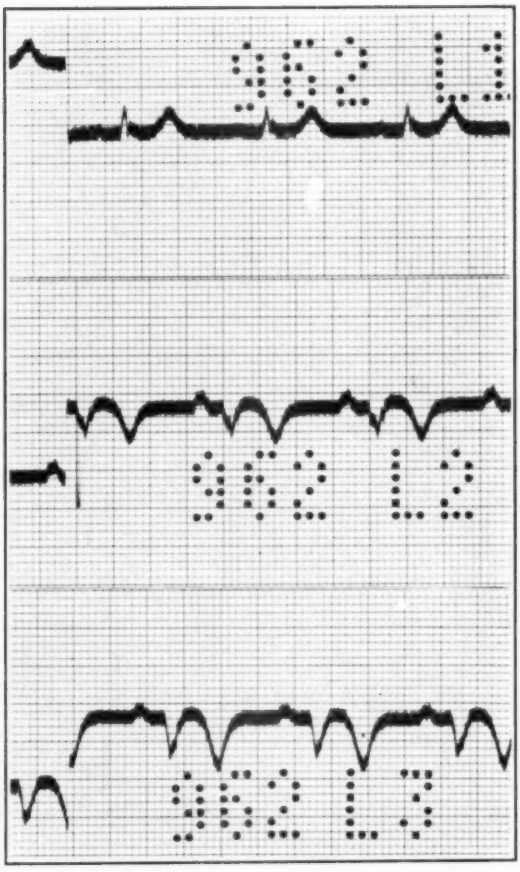

FIG. 4.—From same patient taken, March 14, 1930.

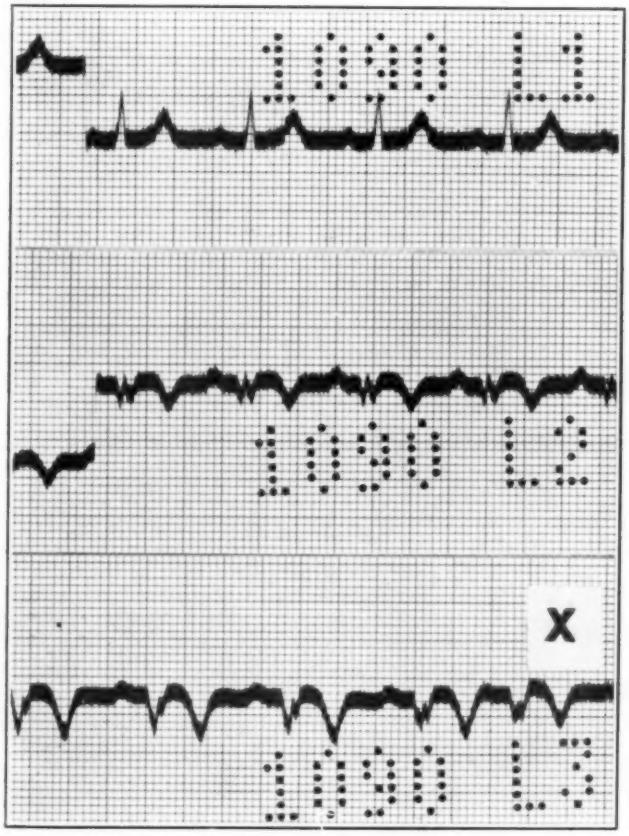

FIG. 5.—From same patient taken, May 26, 1930.

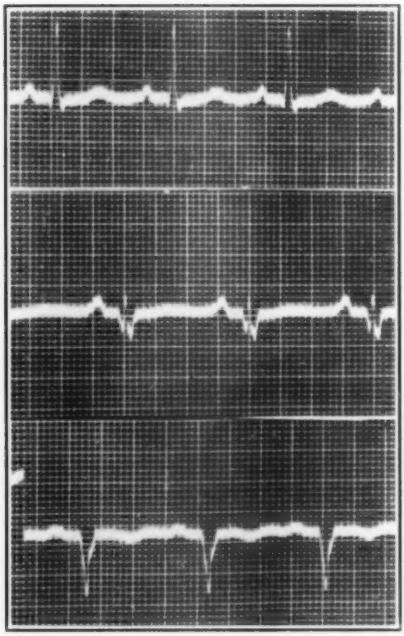

FIG. 6.—Three leads of electrocardiogram, Case II, taken on January 11, 1929.

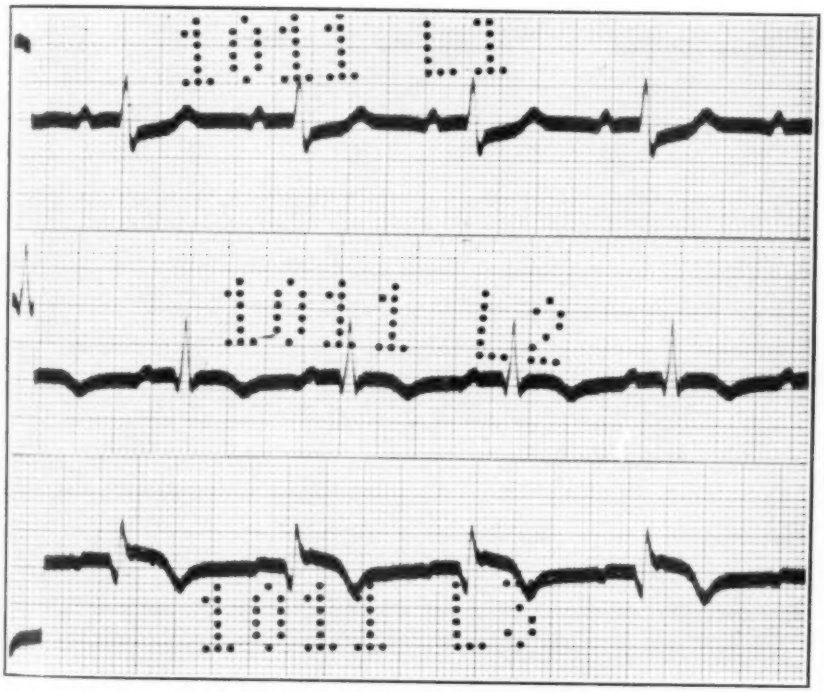

Fig. 7.—From same patient taken, April 8, 1930

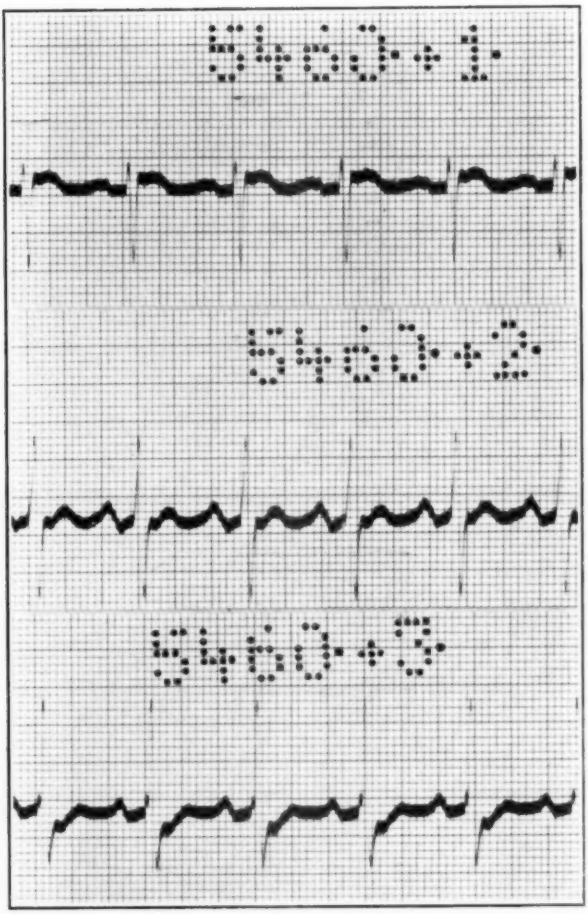

FIG. 8.—Three leads of electrocardiogram, Case III, taken on June 18, 1930.

this away and felt very restless. The room seemed stuffier all the time. He then noticed that his left arm between the elbow and wrist ached, and he massaged it to take the cramp out. While he was doing this he had a smothering sensation and felt as though he was going to faint. The perspiration broke out over his body, and he then thought that he was going to die. He remembers being moved to the next room but remembers nothing of his ride to the hospital.

He had had periodic health examinations but was always found in good physical condition.

On admission to the hospital the patient was in evident shock. His skin was cold and clammy, he was unconscious and his respirations were labored. His heart was not enlarged and the blood pressure was 80 systolic and 30 diastolic. There was a cardiac arrhythmia with a pulse deficit, the rate being about 55. The heart sounds were of poor quality. There was no edema. Examination was otherwise negative. An electrocardiogram (Fig. 1) was taken immediately on admission (two and a half hours after the attack). No medication was given except morphin.

February 11: The patient was conscious, but very restless in spite of considerable morphin. He vomited undigested food which he had eaten twenty-four hours previously. He appeared generally worse, although the shock had largely disappeared. An electrocardiogram was taken in the morning (Fig. 2). In the evening the patient had an enema and voided for the first time. At this time the blood pressure was 118 systolic and 70 diastolic. A small friction rub was heard over the mitral area. The veins in the neck were less distended than on the previous day. The urine showed a trace of albumin and many granular casts and a few red blood cells. The white blood count was 28,200 and the temperature was 38° C.

February 12: There was a marked friction rub over the mitral area. Blood pressure was 102 systolic and 58 diastolic. The patient complained for the first time of a heavy feeling over the sternum. Extrasystoles were less frequent and the heart had a dominant rhythm.

From this date on his condition rapidly improved, the friction rub rapidly disappeared, the casts, red cells and albumin disappeared from the urine, the pulse became stronger, the extrasystoles less frequent and the patient much stronger physically. On March 1 the heart appeared perfectly normal. The temperature which had been 38° C. came down to normal on February 16. The patient was discharged on March 15.

During his stay in the hospital frequent electrocardiograms, 18 in all, were taken. Following his discharge three further records were made, the last about a month before the patient's death. The patient toppled over and died suddenly on June 20 while walking into his office. No autopsy was obtained.

Comment. The clinical history of this case is very typical of an acute coronary thrombosis with myocardial infarction, as is also the mode of death. The electrocardiograms obtained bear out this interpretation. They show the typical *R–T* deviations, which are seen following such an accident. Immediately following the attack there develops an auricular fibrillation, with a marked monophasic curve replacing the usual *Q–R–S–T* complex (Fig. 1). This monophasic deflection is largest in Lead III. It is upright in this lead, is preceded by a tiny inverted spike and fibrillary oscillations distort its rising top. In Lead I the monophasic curve is inverted and preceded by an upright spike. The ventricular complex in Lead II

has a normal configuration except for the negative *S–T* interval and the low amplitude of the *R*. The abnormality of the ventricular complex in Lead III is as marked as any we have seen reported in the literature.

Within twelve hours the configuration of the electrocardiogram alters greatly to give the more usual type of *R–T* deviation associated with coronary thrombosis (Fig. 2). At this time the mechanism is normal, except for a sinus arrhythmia, an occasional auricular extrasystole (in Lead II) and temporary *A–V* dissociation with the ventricular rhythm faster than the auricular (*D* in Leads I and II). The *S–T* interval in Lead I has become less negative and is now followed by a positive *T*. The *Q–R–S* in Lead II has become inverted and split in two and the *S–T* interval has become positive in this lead. In Lead III there is now visible a small, notched and inverted *Q–R–S*, followed by a positive *S–T* interval.

Eight days later (Fig. 3) the electrocardiogram is very similar to the one previously taken, except that the idioventricular rhythm is no longer present. Auricular extrasystoles are still present.

In the next three months, for example, Figs. 4 and 5, the *Q–R–S* in Leads II and III has become smaller and broader; the *S–T* interval has become isoelectric; the *T* wave has become deeply negative and cove shaped in Leads II and III, so that it dominates the electrocardiogram. The *T* wave has become larger in Lead I. A nodal extrasystole is recorded in Fig. 5 (indicated by an X).

The interesting thing, it seems to us, is the rapid change in the electrocardiogram in the first twelve hours, that is, between Figs. 1 and 2, as compared with the relatively slow change in the next three months, that is, between Figs. 2, 3, 4 and 5. The sudden failure of the heart—resulting from the coronary occlusion, and evidenced by the appearance of a shocklike condition and an unusually low blood pressure—would in itself cause a diminution in the coronary flow. This general lessened coronary flow, leading as it does to a myocardial ischemia, explains the marked difference between the curves of Fig. 1 and Fig. 2. Fig. 2 expresses the effect of the coronary occlusion *per se* with an almost normal left ventricular pump and systemic blood pressure. The superimposed bizarre configuration of Fig. 1 is the result of an added general myocardial ischemia which the lowering of blood pressure and the incompetence of the left ventricle induces.

Case II.—A man, aged seventy-two years, entered the hospital on January 10, 1929, with a complaint of having had attacks of substernal pain for the past five or six months. These attacks were brought on by exertion, a big meal, or emotional disturbances. The night before his admission he had a very unusually severe attack of substernal pain accompanied by shortness of breath, cyanosis and severe shock. Physical examination at this time revealed a very obese male, aged seventy-two years, lying in bed somewhat short of breath, with a tinge of cyanosis. The radial arteries were quite sclerotic, the heart was not enlarged, heart

sounds were normal but distant, the blood pressure was 140 systolic and 74 diastolic. There was no edema, and the edge of the liver was just palpable. Examination otherwise was negative. An electrocardiogram was taken the next day (Fig. 6), and the patient was discharged.

On January 15, four days later, the patient was readmitted to the hospital, where he stayed until February 21. During this time he had mild attacks of substernal pain which at times ran down the left arm. Amyl nitrite gave him relief during these attacks. His blood pressure at this time was 140 systolic and 80 diastolic. The urine was negative, the hemoglobin was 90 per cent and the white blood cell count was 7400. The attacks came farther apart, and the patient was discharged on February 21, practically free of attacks. No electrocardiograms were taken during this period.

On April 8, 1930, the patient was readmitted to the hospital in an unconscious state at 5 A.M. About midnight the evening before he had had a very severe attack of substernal pain which led to a general collapse. During the attack he was very cyanotic, short of breath and cold and clammy with cold perspiration. When seen in the hospital the patient was completely morphinized, but had received no other medication. The patient was very cyanotic, respirations were very labored, his blood pressure was 112 systolic and 60 diastolic. His skin was cold and clammy and the extremities were very cold. The heart rate was 70 and the pulse of poor volume. A diagnosis of acute coronary thrombosis was made, and at 9.15 A.M. an electrocardiogram was taken (Fig. 7). The patient never regained consciousness and died at 3.30 P.M.

Autopsy. (Inspection of the thoracic organs only.) Excerpt of report by Dr. R. Dominguez: The body is that of an adult white male, well developed, obese. There are no external abnormalities except marked engorgement of the veins of the neck and slight cyanosis of the face. The *lungs* are emphysematous and moderately anthracotic.

The *heart* is considerably dilated. The wall of the left ventricle at the apex is very thin. The epicardial fat is abundant, especially over the right side. Multiple sections of the left ventricle show an old infarction involving fully one-third of the left ventricle at the apex. Under the epicardium there are a few areas of fibrosis, especially in the right ventricle. There is no recent infarction. The valves are all normal, except for a moderate fatty infiltration of the large mitral cusp. The coronary openings are both patent. The left coronary artery shows a severe arteriosclerosis with calcification of the wall and marked narrowing of the lumen at the base of the descending branch. The diseased portion is not quite 2 cm. in length. There is no recent thrombus in the vessel. The right coronary is sclerotic, but to a much less degree than the left. There are no mural thrombi in the ventricles or auricles. The ascending portion of the arch of the aorta is smooth.

Microscopic Examination. Sections from the left coronary at the diseased portion shows an obliteration of the lumen by an old organized and vascularized thrombus. Around the new-formed capillaries there is a moderate round-cell infiltration. In some areas toward the periphery there are coarse granules of hemosiderin. In another area there are calcium deposits. The muscularis is thin. There is no infiltration of the adventitia. The heart muscle at this level shows a discrete fibrosis. Another section shows the same obliteration of the coronary, but somewhat more extensive changes in the myocardium. Sections from the base of the heart show practically no abnormality. Sections from the area of infarction show a variety of lesions which can be interpreted as the different healing stages of multiple old minute anemic and hemorrhagic infarctions.

Pathologic Diagnosis. Arteriosclerosis of coronary arteries, patchy, especially marked in the left coronary. Organized thrombus of left coronary

artery. Multiple old anemic and hemorrhagic infarctions of the myocardium of the left ventricle. Hypertrophy and dilatation of the heart.

Comment. This is a case of a coronary thrombosis which occurred apparently more than a year before the patient died. At that time his electrocardiogram showed nothing diagnostic of such an accident (Fig. 6). True, there is evidence of myocardial pathology in the notching and duration of the *Q–R–S*, which latter was at the upper limits of normal (0.1 second), in the low *T* waves in Leads I and II and in the inversion in Lead III, but there is nothing which is pathognomonic of an acute coronary thrombosis.

On the other hand, in the patient's final days he develops what appears clinically to be a typical acute coronary occlusion leading to his death. An electrocardiogram taken at this time (Fig. 7) shows the typical *R–T* deviations associated with coronary thrombosis, namely: a negative *S–T* in Lead I, a slightly positive *S–T* in Lead II with a small negative cove-shaped *T* following, and in Lead III a more striking positive *S–T* and deeper cove-shaped *T*. Yet a thorough examination of the heart at autopsy failed to reveal any evidence of a recent fresh coronary thrombosis or recent myocardial infarction. There was definite evidence of an old occlusion which had been partially recanalized and there was present an old organized infarct, but there was no recent coronary pathology.

It seems to us that a case such as this illustrates how a generalized myocardial failure, arising independently of any coronary thrombosis, can lead to electrocardiographic changes characteristic of coronary occlusion when the myocardial failure is associated with severe interference with the coronary flow, due to a marked narrowing of these vessels.

The two cases just presented indicate: (1) That the muscle failure associated with sudden coronary occlusion plays its part in changing the ventricular complex of the electrocardiogram; (2) that the electrocardiogram of a sudden coronary occlusion may be simulated by myocardial incompetence superimposed on a marked organic narrowing of the coronary arteries, even in the absence of a fresh thrombosis in the arteries. Incompetence of the heart with its consequent myocardial ischemia, therefore, has a great influence on the electrocardiogram.

CASE III.—The patient, aged twelve years, was admitted to the hospital on June 12, 1930, complaining of pain around the heart for the past month, associated with vomiting and pain in the epigastrium after eating. Last fall the patient suffered from frequent sore throats. Soon after this he experienced pains in various joints. His parents did not remember whether or not this was accompanied by fever. The tonsils were removed in the spring because of the frequent sore throats. A month after this he experienced pain around his heart, which was intermittent. Eight days before admission the precordial pain become more severe. Since then the pains and vomiting have continued. He had been unable to sleep; his appetite had become poor and he had lost six pounds.

On *physical examination* a dyspneic youngster was found. The mucous membranes and lips were pale and moderately cyanotic. There was marked fullness of the neck with venous engorgement of the superficial vessels. Carotid and venous pulsations were noted. Some impairment of resonance was present at the left lung base posteriorly. Breath sounds were harsh throughout, with occasional râles at right lung base. A definite harsh to-and-fro friction rub was heard at the left base posteriorly and in the left axilla. The apex beat was in the sixth interspace; it was forceful, heaving and diffuse. The rhythm was regular and the apex rate 120 per minute. A prolonged whistling crescendo systolic murmur was heard at the apex and was transmitted to the axilla. A prolonged rumbling diastolic murmur was heard over the precordium, especially at the apex and aortic areas. The pulmonic second was markedly accentuated. The cardiohepatic angle was about 90 degrees. Blood pressure was 134 systolic and 40 diastolic. Capillary pulsation was elicited. The liver was four fingers below the costal margin and quite tender; the spleen was palpable. No edema was present. Urine showed some albumin and a few hyalin casts. The red blood cell count was 4,550,000; hemoglobin, 75 per cent; white blood cell count, 18,000. A 6-foot plate showed the transverse diameter of heart equal to 70 per cent of chest diameter, with bowing of auricle and pulmonic curves.

June 15: Child was much more comfortable. Dyspnea was not so marked.

June 18: An electrocardiogram was taken (Fig. 8).

June 19: Temperature subnormal. Pulse around 100, Corrigan in type. Dullness present at right base posteriorly with distant breath sounds. Friction rub heard on both sides.

The patient expired on June 21.

Clinically the patient was considered to have rheumatic pericarditis with effusion, marked cardiac hypertrophy and dilatation, aortic insufficiency and mitral stenosis and insufficiency, bilateral pleurisy with effusion and ascites.

Autopsy. (Excerpt of report by Dr. O. Saphir.) The body is that of a Mexican child, apparently about eleven years of age.

The right pleural cavity contains about 800 cc. of clear straw-colored fluid; the left is free of fluid. The pericardial sac contains 15 cc. of similar fluid and the abdominal cavity contains about 1 liter.

The *heart* is enlarged, completely filling the pericardial sac. The enlargement is due to marked hypertrophy and dilatation of both ventricles, and the heart weighs 300 gms. The right auricular appendage contains several small reddish-gray thrombi which are attached to the endocardium. The tricuspid orifice and valve are normal grossly. The wall of the right ventricle is markedly hypertrophied, measuring 5 mm. in diameter at its thickest point. The right ventricular cavity is widely dilated. The pulmonary valve and artery are normal grossly and no thrombi or emboli are visible in the deeper branches of the artery. The endocardium of the left auricle is somewhat thickened. Along the free edge of the mitral valve there is an even line of small grayish-red vegetations, all about the same size, measuring approximately 1 mm. in diameter. The free edge is somewhat hyperemic and edematous. Similar vegetations are found on all three cusps of the aortic valve which similarly are markedly edematous and reddened. The wall of the left ventricle is hypertrophied and the chamber markedly dilated. The aorta proper shows no gross pathologic changes. On section the myocardium has a peculiar pale, somewhat mottled reddish-gray appearance and occasional tiny white dots and streaks are visible.

Both *lungs* are somewhat firmer than normal and on section are reddish-brown in color. The surface suggests a fine granularity. In the left lower

lobe there is a very firm area, about 3 cm. in diameter, which projects above the surrounding lung tissue and which, on section, is roughly triangular in shape and dark purple-red in color. On the pleural surface over this area there is a small amount of fresh fibrin.

The *liver* is enlarged and quite firm, weighing 750 gms. Both *kidneys* are about equal in size and shape and together weigh 225 gms. Both are much firmer than normal, and on section there is marked contrast between cortex and medulla due to the dark purplish-red color of the bases of the pyramids. The *spleen* is markedly enlarged, purple-red in color and very firm in consistency. On section the splenic corpuscles cannot be made out, due to the diffuse cyanosis of the entire organ.

Microscopic Examination. The heart muscle fibers appear swollen. The cytoplasm appears granular, and the striations in some portions cannot be made out at all. Many sections show connective-tissue fibers, most of which are poor in nuclei. Other fields show an infiltration of endothelial cells, mainly noticeable around small bloodvessels. Some of these cells are distinctly arranged in three or four rows. Between the cells and surrounding them a few lymphocytes and occasional polymorphonuclear leukocytes are seen. The endocardium is markedly thickened and fibrosed and shows in some portions a diffuse infiltration of lymphocytes, endothelial cells and a few polymorphonuclear leukocytes. Throughout the adventitia there is a moderate amount of infiltration of lymphocytes and endothelial cells. These cells do not show any particular arrangement. These changes are found only very close to the aortic valve. The media and the intima show no changes.

Some of the alveoli are filled with red blood corpuscles while others contain many polymorphonuclear leukocytes and a serum precipitate. The outlines of the alveolar walls are clearly recognizable. Many fields show within the alveolar walls endothelial cells which are filled with a brownish pigment. The alveolar walls, in general, are thickened and show an increase in connective tissue. The smaller bronchi similarly contain polymorphonuclear leukocytes.

Pathologic Diagnosis. Acute rheumatic verrucous endocarditis of the mitral and aortic valves. Acute and chronic rheumatic myocarditis. Marked hypertrophy and dilatation of the heart. Mural thrombi of the right auricular appendage. Chronic passive hyperemia of the lungs, liver, spleen, kidneys and gastrointestinal tract. Bronchopneumonia. Pleural effusion (right), ascites, slight pericardial effusion.

Comment. The electrocardiogram shown in Fig. 8 has, in addition to the right ventricular preponderance, a striking alteration in the *S–T* interval, which in Lead I is definitely positive and in Lead III definitely inverted. On the basis of the observations made on man and the dog,[1,2] such changes would indicate, in a child with acute rheumatic fever, that there was a pericardial effusion. Yet at autopsy very little fluid was found (only 15 cc.). The changes must, therefore, be due to some other cause. Two possibilities suggest themselves. It may be that the advanced fulminating rheumatic myocarditis present in this child led to the change. On the other hand, both in life and at autopsy there was present a tremendously dilated heart. And it is not unlikely that under such circumstances the restraining influence of the pericardium acting on this dilated heart, together with the small amount of fluid present in the sac, would have the same "tamponade" effect as a large amount of fluid

with a smaller heart, especially when the heart is incompetent. At any rate, it would appear that under certain circumstances small, almost negligible amounts of fluid in the pericardial sac may produce electrocardiographic aberrations similar to those of a substantial pericardial effusion.

Conclusion. The three cases reported indicate that acute myocardial ischemia depends not only on coronary occlusion and pericardial effusion, but also on the competence of the heart and its dilatation. They also illustrate some of the errors liable to creep into the interpretation of the significance of the so-called "coronary *R–T* deformities."

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DOES CARCINOMA OF THE DUODENUM EVER ARISE FROM DUODENAL ULCERS?

REPORT OF CASES.

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AN attempt has been made to determine whether duodenal ulcers undergo carcinomatous changes, and the literature pertaining to the subject was reviewed with that in mind. In considering carcinoma of the duodenum one must determine: (1) Whether it is a primary carcinoma of the duodenum, that is, without preceding ulcer; (2) whether it arises from the ampulla of Vater; (3) the possibility of aberrantly placed thyroid, pancreatic, parotid or other glandular tissue in the duodenum which gives rise to the malignancy; (4) whether it is a primary growth in the pancreas producing a duodenal deformity simulating an ulcer; (5) an unquestionable chronic duodenal ulcer developing into carcinoma. It is well to consider the division of the duodenum into first, second and third portions, or the supraämpullar, ampullar and infraämpullar parts. It is known that ulcers usually occur in the supraämpullar,

or first part, and carcinoma in the ampullar, or second part. Deaver and Ravdin,[1] in 1920, "Reported a case of duodenal carcinoma originating below the papilla of Vater. There was no evidence of any preceding ulcer in this case. In a review of the literature of duodenal cancer they noted that the second portion of the duodenum is much more liable to be the site of carcinoma than either the first or the third portions. The first portion is, however, 'the favorite site of duodenal ulcer.'"

That primary carcinoma of the duodenum develops is generally admitted. McGuire and Cornish,[10] in 1920, reported 2 cases of primary duodenal carcinoma and 2 others that were primary in the bile ducts with secondary invasion of the duodenum. In their report they quote nine authors that have performed 151,201 autopsies and finding 50 duodenal carcinomas, or 0.033 per cent. Dr. Krumbhaar informs me that in 25,787 autopsy records at the University of Pennsylvania there were records of only 7 primary carcinomata of the duodenum, or 0.027 per cent (and 3 of these might possibly have been primary in the pancreas with duodenal infiltration). In only 1 of the 7 was there any evidence that the carcinoma had developed in the base of the ulcer, but this involved pancreas and duodenum equally.

The following case will illustrate how easily, from the operative findings alone, one can be mislead as to whether we have been dealing with a duodenal ulcer or a primary carcinoma.

Case Reports. CASE I.—A male, aged forty-six years, was admitted, October 24, 1927, complaining of pain in the stomach before and after meals for six months, not relieved by food but by soda bicarbonate. During the past three months he had lost 15 to 20 pounds. Gastrointestinal Roentgen ray examination on October 27 reported carcinoma of the pylorus, with one-third of motor meal retained at the end of six hours. Operation on October 29 showed ulcer of the first portion of the duodenum, ½ inch distal to the pyloric vein; a posterior gastroenterostomy was done. The patient was followed in the gastroenterologic clinic and was symptom-free until April, 1930, when the abdomen became distended and he began vomiting, with loss of weight. Early in July he became jaundiced, and was readmitted, July 25. Roentgen ray examination on June 25 revealed a carcinoma of pylorus, with gastroenterostomy. He was operated upon, July 31, and was found to have a carcinoma of pylorus with general abdominal metastases and biliary obstruction, and a cholecystojejunostomy was done but the patient died, August 1. This case can be considered a primary carcinoma of the duodenum which was not recognized at the time of the first operation. From the history, Roentgen ray examination and subsequent course there is nothing to indicate a duodenal ulcer except the operator's findings.

In view of the gradual transformation of the mucosa of the pylorus and first portion of the duodenum, one wonders why carcinoma of the duodenum is not more frequently seen. Piersol[12] states: "The transitional or intermediate zone connecting the pyloric and adjoining portions of the stomach contain both forms of glands,

those of the fundus variety, with parietal cells being intermingled with the pyloric type. Toward the intestine the change of the pyloric glands into those of the duodenum is gradual, the gastric tubules sinking deeper until, as the glands of Brunner, they occupy the submucous cast of the intestine. . . . The clear, low columnar cells lining the duodenal glands are probably identical in nature with those of the pyloric glands, the variation in size and granularity sometimes observed depending upon differences in functional conditions." Fig. 1, which is a reproduction from Piersol's *Anatomy*, illustrates this transformation.

Eusterman, Berkman and Swan,[4] in 1925, reported "15 cases of carcinoma of the duodenum from the Mayo Clinic. Of these, 6 were in the supraämpullar portion, 6 in the ampullar and 3 in the infraämpullar portion. The mode of onset was gradual in 7 cases, and sudden in 8. In the majority of cases the syndrome of duodenal ulcer was apparent, but the onset of the disease in later adult life, its rapidly progressive character, as a rule, the presence of marked pyloric obstruction and the frequent subacid or anacid gastric contents, and, finally, the general appearance of the patient implied . . . a more serious process. In no case was any evidence presented that the cancer originated in an ulcer."

Herman and von Glahn,[6] in 1921, reported "a case of carcinoma in the supraämpullar portion of the duodenum. Neither the clinical history nor the pathologic findings indicated the existence of a duodenal ulcer preceding the development of carcinoma in this instance. From their observations in this case and a review of the literature, Herman and von Glahn concluded that the relation of duodenal carcinoma to duodenal ulcer is uncertain, 'but certainly carcinoma of the supraämpullar portion of the duodenum may occur independently of ulcer.'"

Cases of carcinoma arising in the ampulla of Vater are more frequently encountered than in any portion of the duodenum. Schofield[13] reports "a case of duodenal cancer in the ampullar region in which neither the clinical history nor the pathologic findings indicated that it had any relation to a preceding ulcer. He concludes from his review of the subject that 'duodenal ulcer has not been clearly proved to be a predisposing cause of duodenal cancer.'"

Lichty,[9] in 1918, stated that "in a series of 486 cases of duodenal lesions, 6 lesions were found to be cancerous and 480 benign ulcers. In 780 cases of gastric lesions, 240 were found to be cancerous and 540 benign ulcers. In the duodenum the cancer usually had its origin either in the pyloric ring (2 cases) or at the papilla of Vater (4 cases), whereas, according to Moynihan, 90 per cent of the ulcers are in the first 1½ inches of the duodenum. Apparently, then, the cancer-bearing areas and the ulcer-bearing areas do not coincide in the duodenum as they do in the stomach."

Disque,[3] in 1922, reported: "A case in a man, aged sixty years, in which a diagnosis of duodenal ulcer was made on the basis of the clinical and Roentgen ray examination; occult blood was constantly present in the stools. At operation a deep ulcerative lesion with hard edges indicating tumor formation was found in the middle portion of the duodenum, just above the papilla of Vater. It had perforated and the pancreas was involved in the growth. There were also metastases in the liver, so that the diagnosis of cancer was easily made. A gastroenterostomy was done, but the patient developed jaundice, apparently due to obstruction of the papilla of Vater by extension of the growth, and died. No autopsy was permitted." Disque reported this as a case of "carcinomatous ulcer of the duodenum."

The following case is reported to illustrate a carcinoma found at the ampulla of Vater in a patient dying from chronic mercurial poisoning.

CASE II.—A male, aged thirty-three years, was admitted on June 2, 1930, with jaundice, fever and leukocytosis. On admission a diagnosis of acute cholecystitis and choledocholithiasis was made, but the patient was found to be suffering from a chronic mercurial poisoning and was treated for same, with marked improvement. After six weeks the patient's jaundice had nearly disappeared, and he was symptom-free when he suddenly developed fever and the jaundice became more marked. After two more weeks of treatment, thinking we might be mistaken in the diagnosis, a laparotomy was performed, and the liver was found markedly enlarged and friable, with a slightly thickened gall bladder. Common duct and duodenum were negative to palpation. The patient died one week later from cholemia. An autopsy revealed toxic changes in the liver and kidneys, and mercury was recovered from both organs. A growth was found at the ampulla of Vater, but the common duct was not obstructed. The primary cause of death was a mercurial poisoning and the duodenal lesion was incidental (Figs. 2 and 3).

Aberrantly placed glandular tissue is found in the duodenum. McGuire and Cornish[10] state: "Pancreatic rests are found in 1 per cent of autopsies." Although no recorded cases of carcinoma of the duodenum arising in aberrant glandular tissue were found, this must be considered a definite possibility in duodenal carcinoma.

That duodenal cancers may have their origin in the pancreas and produce a duodenal lesion simulating an ulcer seems quite probable. The following case is reported, although one is unable to state definitely whether it arose from the pancreas or from a chronic duodenal ulcer.

CASE III.—A male, aged sixty-two years, was admitted on June 17, 1930. Chief complaint, pain in epigastrium for two months. Past history, no serious illness or surgical operations. Habits, smokes 20 to 30 cigarettes daily and drinks occasionally, usually whisky. Present illness, patient states he has been well until two months ago when he began suffering with pain in the epigastrium and with eructations. The pain began in the

right upper quadrant near the midline and radiated to the back on both the right and left side of the spine, extending up as high as his scapula. The pain comes on about four hours after breakfast and about the same time after lunch and he is also awakened about 2 A.M. The pain is relieved by alkalis and somewhat by pressure over the epigastrium. He has never vomited, but his bowels have always been very constipated, and during the past two months he has noticed tarry stools. Appetite is good, but the patient is afraid to eat as it causes him pain. During his illness he has lost 15 to 18 pounds in weight. Physical examination is negative except for abdominal findings. No definite masses can be palpated, but there is localized tenderness in the midepigastrium, and the patient complains of pain which goes through to his spine, and there is slight costovertebral tenderness. Clinical impression, carcinoma of the stomach. Laboratory findings, June 18: Urinalysis negative; white blood count, 10,000, with 55 per cent neutrophils; red blood count, 3,500,000, with 55 per cent hemoglobin; blood chemistry: Nonprotein nitrogen, 35 mg.; creatinin, 2.4 mg.; sugar, 90 mg. Wassermann, negative. After four gastrointestinal Roentgen ray examinations a diagnosis of ulcer of the first portion of duodenum was made without any evidence of malignancy of the stomach and no six-hour residue. On June 24 barium enema showed no organic lesions of the colon. On June 28 cholecystography was reported; the gall bladder was not definitely visualized. On June 26 a note was made by the house physician: "Patient is suffering considerable pain at night which causes him to awaken about 2 A.M., pain being in midepigastrium and radiating to the back. The patient has complained of pain every night since admission. Impression: Penetrating ulcer of duodenum." Surgical consultation was held on July 3. The patient has been vomiting for twenty-four hours and is very emaciated, complaining of severe abdominal pain which radiates to his back. Examination does not reveal any abdominal masses, but there is a localized tenderness in midepigastrium and costovertebral tenderness. Diagnosis: Penetrating ulcer of the posterior wall of the duodenum, associated with chronic pancreatitis. The patient was given 3 per cent glucose hypodermoclyses daily, and a transfusion the day before operation. He was operated upon, July 11, by Dr. W. T. Doran, under spinal anesthesia. The abdomen was opened through a right rectus muscle-splitting incision, and there was found a mass involving the pylorus which was felt to be malignant, as it was firmly fixed. There were no available glands for biopsy and no nodules felt in the liver. Due to the patient's extreme condition a posterior gastroenterostomy was then done without clamps. Postoperative course: The patient declined in spite of supportive measures, and died on July 20, 1930.

Autopsy Findings. (Reported by Dr. D. Symmers.) "In the first portion of the duodenum there is a hard nodular, faintly cream-colored mass which is centrally ulcerated and which measures 6.5 cm. in diameter. It projects into the lumen of this portion of the gut in somewhat mushroom fashion, and appears to be directly continuous with the outer 2 or 3 cm. of the head of the pancreas, which is enlarged and increased in consistence. The rest of the head of the pancreas and, in fact, the balance of the organ as a whole are of normal consistence. Microscopic examination of tissue removed from various parts of the tumor shows the presence of a richly cellular and abundant connective-tissue stroma, scattered through which are innumerable acini of variable shapes and sizes. The individual acinus is lined by a single row of high cuboidal or low cylindrical epithelium, the cells being arranged on their basement membrane in more or less regular fashion. In some instances, however, the cells are heaped up into rows of two or three, while in other instances they may be so abundant as completely to fill the lumen, and thus to appear as a solid mass of cells. Although the

histology of the tumor is characteristic of the cylindrical-cell adenocarcinoma springing from the pancreatic ducts and reproducing them in typical fashion, the presence of a large mushroom-like tumor projecting itself into the lumen of the duodenum and simulating a primary growth of that region is, in my experience at least, a most unusual finding, and constitutes, perhaps, the outstanding feature of this particular case" (Figs. 4 and 5).

Carcinoma arising from chronic duodenal ulcers have been reported, but those cases considered as such seem very questionable on reviewing the reports.

Jefferson,[7] in 1916, reported "a case in a man, aged fifty-five years, who was operated upon for duodenal ulcer (gastroenterostomy). The hospital record stated that a duodenal ulcer was found and the surgeon who performed the operation regarded the condition as 'an ordinary nonmalignant lesion.' Symptoms were relieved until the early part of 1914, when the patient began to lose weight and strength and later developed a troublesome diarrhea. He died on April 5, 1915. Autopsy showed carcinoma of the suprapapillary duodenum extending into the head of the pancreas. It was situated about 2.5 cm. from the pyloric sphincter; it was an annular growth completely obstructing the lumen of the duodenum, with a smooth nonulcerated surface. There was no sign of any preceding simple ulcer, so that if this carcinoma had been implanted upon an ulcer it had destroyed all signs of such an origin." Jefferson was of the opinion, however, that in this case the carcinoma was engrafted on a simple ulcer.

Judd,[8] in 1919, stated "that he was unable to find in the records of the Mayo Clinic any evidence that a primary carcinoma of the duodenum arose from an ulcer."

Haberer,[5] in 1919, reported "one case in which the symptoms were typical of duodenal ulcer and relatively mild, except for the constant appearance of blood in the stool. This bleeding increased until the patient lost some weight and strength. At operation a duodenal ulcer was found, in one section of which there was definite carcinomatous degeneration; there was also a small metastatic growth on the lesser curvature of the stomach. Symptoms recurred about a year after operation and the patient died a little over a year later."

Orator,[11] in 1925, reported "a case in which symptoms present for two years were typical of peptic ulcer. In the latter year the symptoms had become increasingly severe. Roentgenologic examination indicated a duodenal ulcer. At operation two ulcerative lesions were found just below the pylorus, one on the anterior and one on the posterior wall; both proved to be adenocarcinoma. Histologic examination showed also that the mucosa of the pyloric portion of the stomach had extended into the duodenum, and that this was the site of origin of the carcinoma. The clinical history

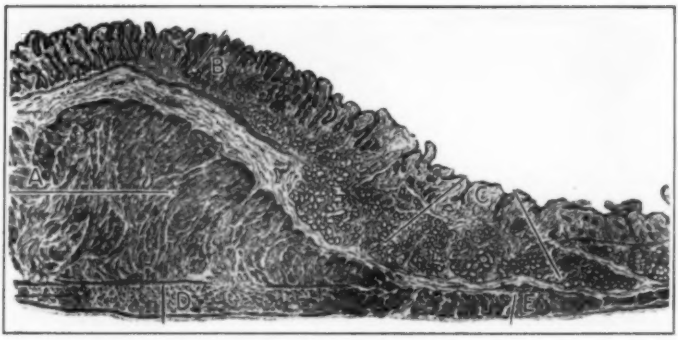

FIG. 1.—Reproduction from Piersol's anatomy, *A*, circular muscle forming pyloric sphincter; *B*, pyloric glands; *C*, Brunner's glands; *D*, stomach; *E*, duodenum.

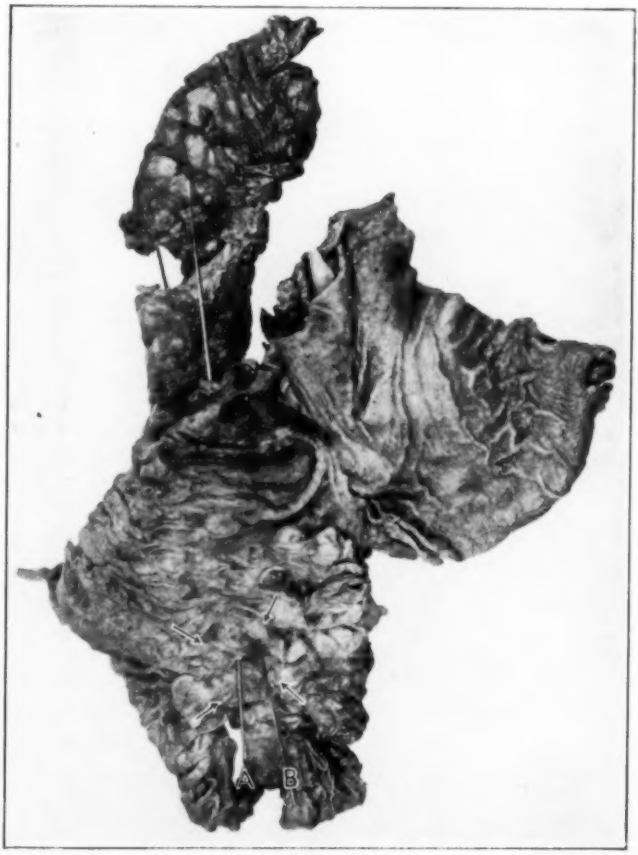

FIG. 2.—Tumor seen arising around ampula of Vater. *A*, probe in common duct; *B*, probe in duct of Wirsung.

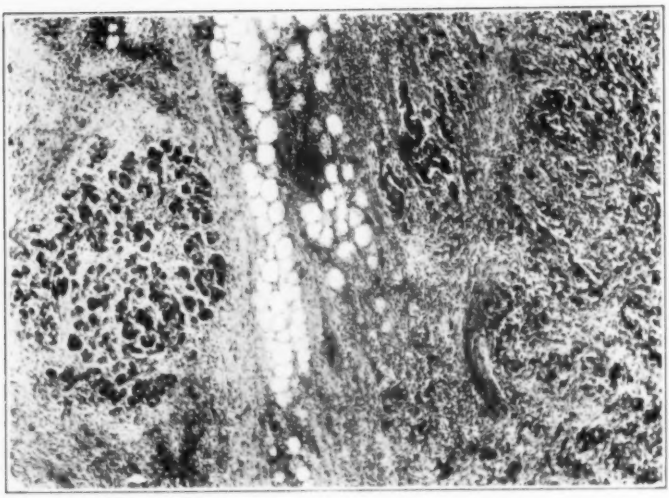

FIG. 3.—Histologic section reveals the tumor adenocarcinoma.

FIG. 4.—Ulcerating area seen in first portion of duodenum. *A*, probe in common duct; *B*, pylorus; *C*, normal duodenum.

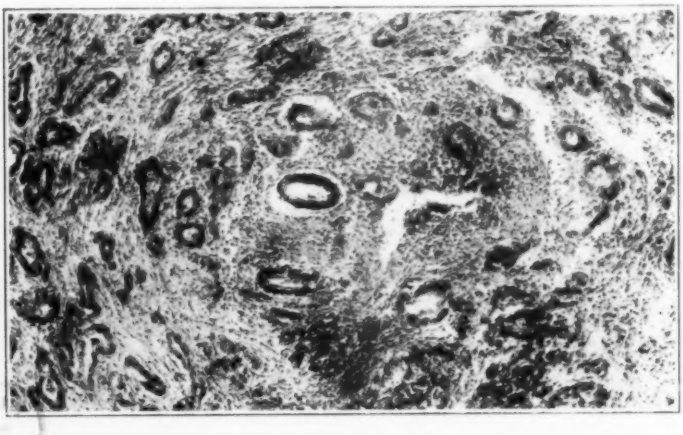

FIG. 5.—Histologic section reveals the ulcerating area adenocarcinoma.

and the changes in the pyloric mucosa indicated that the carcinoma in this case had originated in a peptic ulcer, but this could not be definitely proved."

Dewis and Morse,[2] in 1928, reported "12 cases of carcinoma of the duodenum, 5 of which were in the first portion. In 1 of their cases, that of a man, aged sixty years, a pre-operative diagnosis of pyloric cancer was made because of sudden onset of symptoms and absence of free hydrochloric acid in the stomach. At operation no cancer of the pylorus was found, but a chronic ulcer of the duodenum definitely below the pyloric ring with an inflamed and indurated border, but no definite evidence of malignancy. A gastroenterostomy was done. This operation relieved symptoms and the patient gained in weight. But occult blood in the stools persistently increased; this, with a study of other cases of duodenal cancer, led to the conclusion that 'the ulcer in the patient was really cancer.' At a second operation at the site of what had appeared to be simple ulcer at the first operation, a discrete firm mass, about 2 cm. in diameter, was found. The first part of the duodenum and the pylorus were removed. Histologic examination showed adenocarcinoma of the duodenum, 'scirrhous for the most part, but growing rapidly in places.' The patient made a good recovery, and has shown no recurrence of symptoms."

This is not regarded as a case of cancer arising in a benign ulcer, however. Dewis and Morse believe that the lesion was malignant from the first. The lesion found at the first operation, it is true, "felt and looked like that of benign ulcer." It had a diameter of 2.5 cm., which was rather large for a nonmalignant ulcer, but the bases of simple ulcers may have larger diameters. "It was difficult to adjust a diagnosis of benign ulcer to the results of clinical and laboratory investigations—it could hardly be done. The doubt that lingered led to further study, a definite diagnosis of cancer of the duodenum, a second operation, and, we hope, a cure."

Dewis and Morse also regarded Jefferson's case as being "carcinoma from the outset."

Comment. It would seem that Case III comes nearer to establishing proof that chronic duodenal ulcers can undergo carcinomatous changes than any of the reported cases, but this case may really be a primary pancreatic lesion producing the duodenal deformity secondarily.

Symmers has no recorded case of carcinoma arising in a duodenal ulcer in over 15,000 autopsies at Bellevue Hospital. None of the reported cases of duodenal ulcers developing carcinoma that I reviewed have definitely proven that such changes took place. Undoubtedly this complication can arise, but in view of the frequency of duodenal ulcers this complication can, for a clinical consideration, be excluded in considering the treatment of duodenal lesions. It would seem that most of the reported cases have really

been primary carcinomas of the duodenum, or have arisen from the ampulla of Vater, or the pancreas.

Summary. 1. During the years 1928, 1929 and 1930 there were 324 ulcers admitted to the Gastroenterologic Clinic of the Fourth Medical and Surgical Divisions of Bellevue Hospital. Of this number, there were 269 duodenal lesions, 34 gastric, 14 pyloric and 6 double ulcer, meaning a lesion in the stomach and duodenum.

2. With the marked frequency of duodenal ulcers, it is difficult to explain why these cases do not undergo carcinomatous degeneration.

3. Primary carcinoma of the duodenum is occasionally seen.

4. Clinically one can disregard the possibility of a duodenal ulcer ever taking on malignant degeneration.

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THE NATURE OF THE SYMPTOMS IN ESSENTIAL HYPERTENSION.*

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The clinical entity, essential hypertension, was described by Mahomed[1] as early as 1879. In the studies of this brilliant clinician attention is called to the occurrence of certain symptoms. "Persons

* The present study was carried out in the Medical Clinic of the Boston Dispensary during the years 1927–1929.

who are subject to this condition suffer from many of the minor ailments which are characteristic of individuals who are the subject of chronic Bright's disease,[2] such as malnutrition, cold hands and feet, shortness of breath and palpitation on exertion, imperfect digestion, bronchial and gastric catarrh, headaches (especially hemicranial), sometimes tinnitus and dimness of vision." He noted that such complaints often dated back to early life, and he felt that the symptom picture was so characteristic as to suggest the presence of the underlying hypertension. In 1926 Kauffmann[3] expressed a similar stand in respect to the diagnostic character of the patient's complaints.

Symptoms associated with the early stages of hypertension have not always been clearly differentiated from those due to complicating diseases such as arteriosclerosis with its involvement of cerebral, cardiac, and renal arteries. It is interesting that Clifford Allbutt[4] maintained that the only symptoms of hypertension were those of its complicating diseases. However, numerous clinicians writing on various aspects of the problem have made frequent reference to symptoms seen in the early stages of hypertension at a time when complicating disease is unlikely. Treatment has often been directed against these symptoms and the value of medication in hypertension gauged by the relief obtained. Studies by Kauffmann[3] Schultz and Biehn,[5] Paullin, Bowcock and Wood,[6] Douthwaite,[7] Ohler,[8] Rolleston,[9] and Riseman and Weiss,[10] have dealt with the nature of the somatic complaints in the disease.

In the present communication, evidence is offered to show that the symptoms generally occurring in patients with uncomplicated essential hypertension are those of an associated psychoneurosis: (1) A psychoneurosis is shown to be present in these patients; (2) a comparison of their symptoms with those of a control group of neuropaths without hypertension, shows agreement in character, frequency, duration, course and influence by suggestion and sedatives.

The evidence that the symptoms seen in essential hypertension are not due to the increased intraärterial tension, *per se*, has been stated from time to time and may be summarized as follows: (1) An elevation in blood pressure is not infrequently found in individuals who complain of no symptoms; (2) the appearance of symptoms is often noted at an early age, when blood pressure is either normal or only slightly raised; (3) the height of blood pressure and the presence of symptoms do not show the degree of correlation that would be expected if a causal relationship existed. For example, the symptoms are neither more frequent nor more marked in patients with high elevation than in those with lower pressures.

The distinction has been made between symptoms present in the early stages of hypertonia and those appearing later as a result of complicating vascular changes. The present study is concerned only with symptoms present before the onset of complicating dis-

ease. There is evidence that when hypertension has been present for a number of years it is associated with vascular changes. Particularly, in so called malignant hypertension, where the elevation is persistently high is this true. It is known that sclerotic changes may give rise to certain symptoms. For example, vertigo is a common symptom in patients with advanced cerebral arteriosclerosis, and it is not unlikely that headache and dizziness developing late in essential hypertension may be due to such arterial changes. In the present study, however, evidence that the symptoms were of this origin was not obtained. As will be indicated below, the symptoms generally appeared in early life at a time when arterial changes were unlikely.

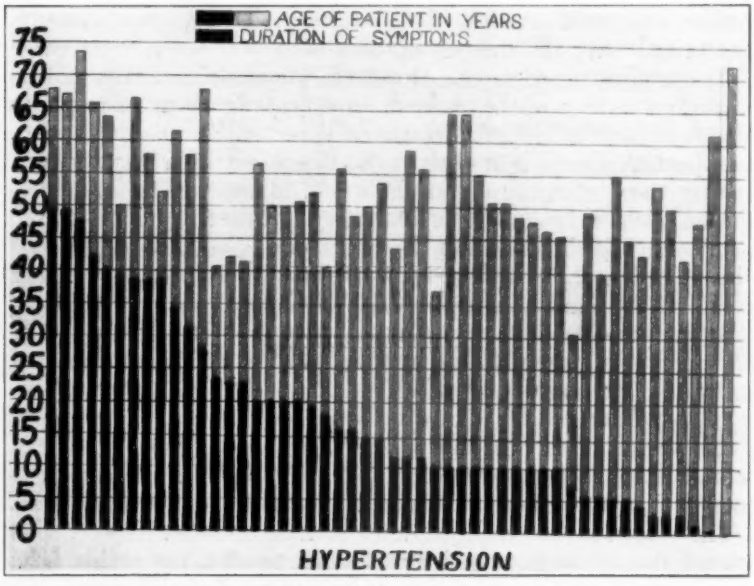

CHART I.—The distribution of the duration of the present illness in 50 unselected patients with hypertension.

The data for the present study were obtained as follows: (1) Records of 100 hypertensive outpatients covering visits in individual cases over a period of from one to seventeen years; (2) individual studies on 53 of these same patients coming under personal observation. Patients with evidence of renal, cardiac or cerebral disease were excluded. All patients showed a systolic blood pressure of 160 or higher, and the records indicated that this hypertension had been present for a period of from one to ten years. Seventeen were males, 83 females. The ages varies from forty-two to seventy (average fifty-five) in the males; from 32 to 74 (average 52) in the

females. Forty-five females were in the age-group forty to fifty-five years. There is the possibility that these symptoms were due to changes incident to the menopause. Against this are the following findings: (1) Of the 53 patients coming under observation, 25 gave a history of symptoms antedating the age of 35 (Chart I); (2) a majority of the female patients gave no objective evidence of a present or recent disturbance in the menstrual function; (3) the duration of the present illness in most of the series was far greater than the usual time stated for menopause changes. Thirty-nine of 53 patients had symptoms for a period greater than ten years (Chart I).

THE SYMPTOMS. Table below gives the symptoms occurring in 100 cases. These represent a composite picture of complaints made over a period of years. They were usually of long duration, persisting for days, weeks, months or years, and were often severe in character. All complaints were not necessarily made at any one visit.

THE FREQUENCY OF INDIVIDUAL SYMPTOMS IN 100 PATIENTS WITH ESSENTIAL HYPERTENSION.

Symptoms.	Per cent present.	Symptoms.	Per cent present.
Headache	72	Epigastric fullness	30
Pain	67	Anorexia	28
"Nervousness"	67	Heartburn	24
"Dizziness"	66	Nausea	21
Fatigue and weakness	65	Palpitation	18
Insomnia	63	Pain over cardiac area	15
Constipation	57	Vomiting	14
Fatigue	55	Tremors	12
Vasomotor symptoms	54	Choking sensation	12
Weakness	38	Cough	9
Parasthesias	38	Bad taste in the mouth	7
"Gas on stomach"	37	Fainting	6
Shortness of breath	34	Loss of weight	6

Table and Chart I, illustrate three general characteristics of these symptoms: (1) They are generally multiple and widespread, being distributed to almost every system and bodily part; (2) certain symptoms, such as pain, headache, constipation, and fatigue, are present in great frequency; (3) the duration of the symptoms is unusually long. Chart I tabulates this duration in 50 patients. It will be noted that 30 complained of symptoms over a period greater than ten years; 25 for fifteen or more years; 11 for thirty or more years. The occurrence of symptoms in the early life of hypertensive patients has been noted by many observers since first pointed out by Mahomed.

Only 4 patients of the series of 100 were entirely without symptoms. In Schultz's series 12.5 per cent were symptom-free. As the patients in the present series came to the clinic, for the most part, because of symptoms, no satisfactory idea of the incidence of symptom-free hypertension can be obtained from these data.

Evidence that Hypertensive Patients With Symptoms Suffer from an Accompanying Psychoneurosis. There is general agreement that a neurosis results from functional as opposed to organic changes. According to most authorities, two factors are operative: (1) A constitutional vulnerability; (2) emotional difficulties resulting from faulty adjustment of the individual to the environment. A person with otherwise adequate constitution is seen to develop a neurosis, when events in the environment are sufficiently unfavorable. On the other hand, relatively minor circumstances may precipitate a neurosis in one with little capacity for adjustment. According to Dejerine[11] the essential factor is the inability to adapt to the demands of the environment.

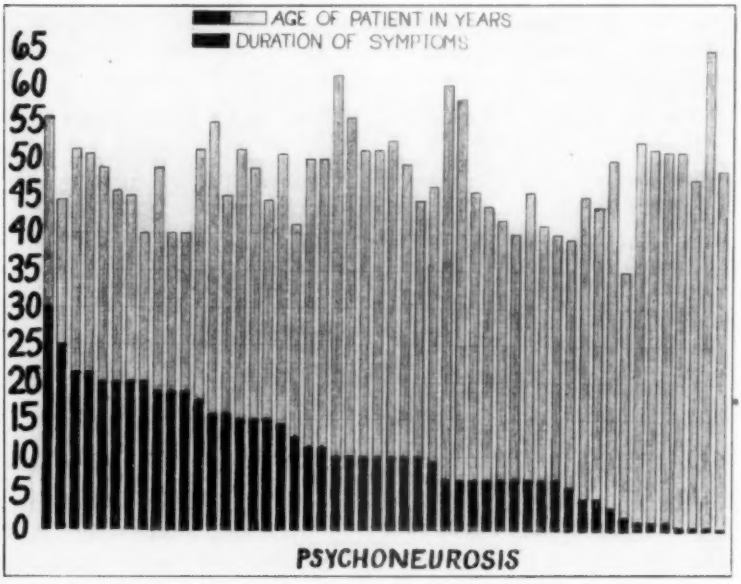

CHART II.—The distribution of the duration of the present illness in 50 unselected patients with a psychoneurosis.

In the present study the diagnosis of psychoneurosis was made when the following conditions were fulfilled: Symptoms characteristic of a psychoneurosis were present; physical examination revealed no organic disease which would satisfactorily account for these symptoms; the emotional history revealed that at the time faulty adaptations occurred, somatic symptoms developed. In a previous study[12] it was noted that the symptoms of a neurosis are often characteristic. Three general aspects were summarized: their multiplicity and widespread character; the high incidence

of such symptoms as pain, headache and fatigue; the unusually long duration of the symptoms.

The entire group of hypertensive patients with symptoms, personally observed, fulfilled the criteria mentioned for the diagnosis of a psychoneurosis. The symptoms were characteristic, the physical examinations negative, and the emotional histories revealed the presence of significant environmental difficulties closely related in time to the appearance or increase in severity of symptoms.

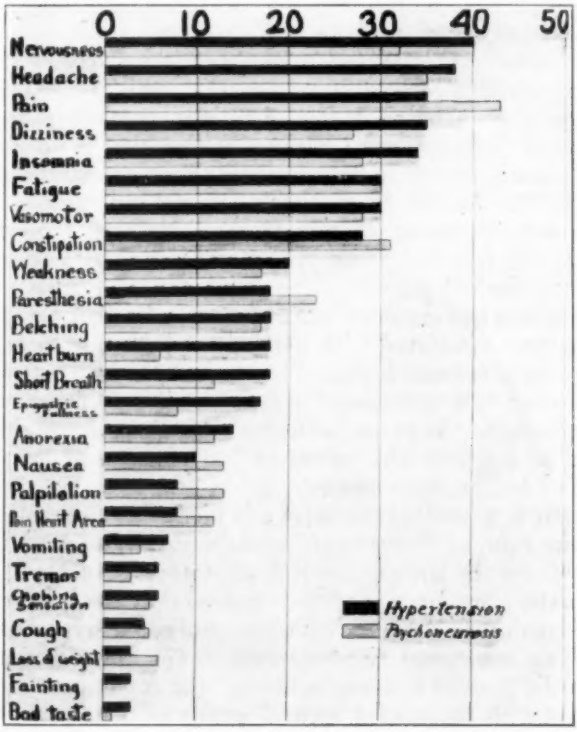

CHART III.—The frequency of individual symptoms in 50 patients with hypertension compared with the frequency of symptoms in a control group of 50 patients with a psychoneurosis.

A Comparison of the Symptoms in Hypertension With Those of a Control Group of Patients With Psychoneurosis. Chart III, compares the symptoms of 50 unselected hypertensive patients (average age fifty-one years) with those of 50 patients suffering with a neurosis (average age forty-eight years). The latter were unselected except for age. It will be noted that the symptoms compare not only closely in kind but remarkably so in their respective frequencies. This is rather striking and suggests that identical mechanisms are

responsible for their production. Headache, dizziness, fatigue and other symptoms occur no more frequently in hypertension than they do in neurasthenia.

In Charts I and II the duration of the present illness may be compared. Here, likewise, there is agreement.

In addition to a comparison of gross aspects the character of individual symptoms may be profitably compared. For example, let us examine fatigue. It is noted (Chart III) that this symptom occurred 30 times in 50 patients with hypertension, and 30 times in 50 control patients with a neurosis. Fatigue is not only common, but so unusually common as to be distinctive.

Three characteristics of the fatigue seen in hypertensive patients are present in the fatigue of neuropaths. (1) The patient often complains of an extreme degree of fatigue, commonly designated by the word "exhaustion." Fatigue of this kind is uncommon in organic disease, except in the presence of advanced disabling disease. (2) The fatigue is, at times, experienced during complete physical rest, appearing often in the morning after a good night's sleep. (3) It frequently disappears when the patient's mind is diverted by work or play.

The Influence of Suggestion and Sedatives. Further evidence that the symptoms associated with hypertension are due to an accompanying psychoneurosis is offered by the known results of suggestion and sedatives. The influence of sedatives in hypertension, especially on the symptoms, needs no comment. It is general experience that they can be lessened with sedatives just as those of neurasthenia are allayed by the same means.

The same is true of suggestion of any kind. The suggestion inherent in any form of "treatment" enthusiastically applied has been responsible for the large number of substances advocated.

Conclusion. Evidence is offered to show that the symptoms generally occurring in patients with uncomplicated hypertension are those of an associated psychoneurosis: (1) A psychoneurosis is shown to be present in these patients. (2) A comparison of their symptoms with those of a control group of neuropaths without hypertension shows agreement in character, frequency, duration, course, and influence by suggestion and sedatives.

NOTE.—I am indebted to Dr. Soma Weiss for first suggesting and stimulating the present study. I wish to thank Dr. Joseph H. Pratt for the opportunity of working in his clinic and for his many helpful suggestions.

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11. Dejerine and Gauckler: Psychoneurosis and Psychotherapy, J. P. Lippincott Company, 1913.

12. Kaplan, Joseph H., and Davis, David: The Incidents of Neurosis and the Character of Its Symptoms. Unpublished Study. Read at the Clinical Meeting of the Boston Dispensary, 1928.

REVIEWS.

CLINICAL INTERPRETATION OF BLOOD EXAMINATIONS. By ROBERT A. KILDUFFE, A.B., A.M., M.D., F.A.S.C.P., Director, Laboratories, Atlantic City Hospital. Pp. 629; 60 illustrations. Philadelphia: Lea & Febiger, 1931. Price, $6.50.

WITH the modern medical emphasis on laboratory methods, it is to be expected that conscientious case studies will include many laboratory reports. But are the requests wisely made by the clinician and the results wisely evaluated by clinician and pathologists? It is still too true that many clinicians know so little about laboratory potentialities and limitations that they either take little stock in it and use it correspondingly or have a blind faith in its omnipotence and in the sanctity of the printed figure. Only the select few know how to utilize it within its proper limitations for maximum results. Such phases of the laboratory problem have received especial attention by the author, which gives freshness and added value to the treatment of a subject about which much has been published in recent years. He has not hesitated to include consideration of some basic principles and various methods of potential but not definitely proven value.

All phases of the clinical laboratory study of the blood are adequately covered—its physical and chemical properties of clinical value; its cytology; the form and function of erythrocytes, leukocytes and platelets in health and disease; the symptomatic blood picture in various diseases; its bacteriology; parasitology and serology; and a long chapter on complement fixation.

Not only should every self respecting hospital laboratory have this book on its shelves but also every clinician who aspires to make the best use of the laboratory that he "uses."

E. K

CALCIUM METABOLISM AND CALCIUM THERAPY. By ABRAHAM CANTAROW, M.D., Assistant Demonstrator of Medicine, Jefferson Medical College, Philadelphia, with a foreword by HOBART AMORY HARE, B. Sc., M.D., LL.D., Professor of Therapeutics, Materia Medica and Diagnosis, Jefferson Medical College, Philadelphia. Pp. 215. Philadelphia: Lea & Febiger, 1931.

A MONOGRAPH reviewing the subject of normal and abnormal calcium metabolism, our knowledge of which has been greatly

advanced by the recent discovery of agents capable of exerting definite effects upon it. Calcium therapy is discussed in detail. In a few conditions this therapy is based on well established physiological principles and yields brilliant results. In many other conditions in which calcium is employed the evidence of its effectiveness is far from convincing. I. S.

THE DOCTOR IN COURT. By EDWARD HUNTINGTON WILLIAMS, M.D. Pp. 289. Baltimore: The Williams & Wilkins Company, 1929.

THE purpose of this book is to advise physic ans concerning their conduct and behavior when called as expert witnesses. The author explains that a physician called to give medical testimony is always an expert—a witness as to opinion, not as to fact. The book is interesting and entertaining, but is written in the twentieth century journalesque style. The author himself says that his doses are sugar coated and explains that "The ordinary legally prepa ed book on forensic, or medico-legal subjects, s certainly an uncoated dose. In delving into such works the physician seldom receives much witness-stand help." The evil of this style of writing is illustrated by the fact that on one page the author states that "sane and innocent people frequently get locked up" and on a later page says "to be perfectly fair to our legal methods, there is very little chance that any really sane man will be placed behind bars permanently." The book is worth reading and easy to read, but a more serious style, and more accuracy in statement would have made it of much greater value. C. B.

HIERONYMUS FRACASTORIUS, HISTORY OF MEDICINE SERIES NO. II OF THE NEW YORK ACADEMY OF MEDICINE. Translation and Notes by WILMER CAVE WRIGHT, PH.D., Professor of Greek in Bryn Mawr College. Pp. 356. New York: G. P. Putnam's Sons, 1930.

THIS book not only coincides with the four hundredth anniversary of the publication of Fracastorius' poem "Syphilis"—his earliest medical work—but inaugurates the new History of Medicine Series being issued under the auspices of the Library of the New York Academy of Medicine. Number 1 of the series, a bibliography of incunabula by A. C. Klebs, is announced to appear shortly. The statement "Copyright, 1930 by Haven Emerson" indicates that our profession now owes another debt of gratitude to that philanthropic physician.

Though Fracastorius' work on Contagious Diseases—published sixteen years after his more famous poem—is vastly more important in the history of medicine than his better known poem, it is here translated into English for the first time. The Latin text, given on the even numbered pages has been revised by Dr. Wright from four of the earliest editions extant; and by an ingenious spacing of type the two texts are made to occupy a closely equivalent space, thus both preserving a more comely appearance and making it easier to find the corresponding word or clause in the other language. We are not competent to form an opinion on the correctness of the text of or the translation; but can express a lively gratitude for the gift of an English version of this work, and for the clear and easy, though somewhat staccato, style. Let us hope that Fracastorius' other medical treatise "De Causis Criticorum Dierum," which the Editor speaks of as Fracastorius' most direct attack on Galen's views, will also soon have similar fortunate treatment.

In a 54 page Introduction, the Editor gives a good backgound for his translation—both in a picture of the times and of the author's life and in an illuminating analysis of the poem, Syphilis. Among the various explanations of the name Syphilis, Dr. Wright favors and adds further evidence for that of Boll, namely that the Author echoed Ovid's tale of Sipylus, son of Niobe. Thus one of the most eminent medical writers of the Renaissance coasts to immortality on a barbarism; while this scientific treatise, which Garrison considers "the first scientific statement of the true nature of contagion," lies buried in the wayside drifts! If this book succeeds in making his worth known to more than the *cognoscenti*, it will doubtless richly repay its editor and inspirer. E. K.

THE GUIDANCE OF MENTAL GROWTH IN INFANT AND CHILD. By ARNOLD GESELL, PH.D., M.D., SC.D., Professor of Child Hygiene, Yale University. Pp. 322; illustrated. New York: The Macmillan Company, 1930. Price, $2.25.

To those aware of the importance of mental hygiene to the present and future generations, a book from the well-known Yale Psycho-Clinic is bound to be arresting and especially when it bears the absorbing title of the one now under review. Disappointment, vague and hard to analyze, accumulates as one progresses through the book. Perhaps it is because too much is expected in a field where science is still groping, perhaps because so many of the chapters have already appeared independently elsewhere that they do not readily fall into a smoothly progressing unity. Nevertheless much of interest and value is to be found within these covers. While the old concepts of child guidance chapter are lavishly delineated,

the eager practitioners in mental hygiene will doubtless hasten through to the more important problems and methods of child guidance, and even perhaps regret that more space had been given to the latter parts, even if at the expense of the historical section.

E. K.

HISTOLOGY FOR MEDICAL STUDENTS. By H. HARTRIDGE, M.A., M.D., Sc.D., M.R.C.P., F.R.S., Professor of Physiology, and F. HAYNES, M.A., Demonstrator of Histology, University of London, at St. Bartholomew's Medical College. Pp. 369; 512 illustrations, New York: Oxford University Press, 1930.

THE interesting feature of this new histology is the extensive use of color illustrations. These are arranged, for the most part, six or eight to the page, and simulate the routine hematoxylin and eosin staining. Although the drawings are small, they are often very successful in depicting the characteristic appearance of the stained tissue.

W. A.

CHRONIC NASAL SINUSITIS. By PATRICK WATSON-WILLIAMS, Hon. Consulting Surgeon in Diseases of the Ear, Nose and Throat, Bristol Royal Infirmary. Pp. 221; 150 illustrations. New York: William Wood & Co., 1930. Price, $5.00.

THIS short monograph was undertaken primarily to expound the author's exploral-suction technique in the diagnosis of nasal sinusitis and intranasal operative methods in its treatment but also provides a brief account of the systemic toxemias and secondary infections of chronic nasal sinusitis. It does not replace the usual textbooks but supplements them by reviewing this phase of the specialty and permitting a general and systematic survey of the sequelæ of chronic nasal sinusitis. The problem of nasal sinusitis in children and of familial infection is well emphasized. It is to be regretted that chronic pulmonary sepsis is dismissed with a brief discussion which does not expound the features of bronchiectasis. Orbito-ocular affections are treated in more detail. The discussion of the technique of endo-rhinoscopy is excellent and this alone will make the volume of value to student and practitioner alike. Transillumination and skiagrams are considered as diagnostic aids but inadequately. The descriptions of pernasal operations offer nothing new. The illustrations, particularly those of nasopharyngoscopic views, are excellent and will be found of great value. The author attains brevity at the expense of thoroughness and leaves one hoping that a later edition will provide the detail which would render the volume unique in its field.

H. S.

CANCER. By WILLY MEYER, M.D., Emeritus Professor of Surgery, New York Postgraduate Medical School. Pp. 427; illustrated. New York: Paul B. Hoeber, Inc., 1931. Price, $7.50.

"THE book consists of 38 chapters, of which the first 29, on the origin, the development and the self-perpetuation of cancer have already been published—(in various journals)—under the heading "Some Notes on Cancer," as individual articles. These first 29 chapters are, however, by no means mere reprints of published articles. All have been revised and expanded to take account of recent work, their sequence has been rearranged, and some have been split up and in part rewritten, so that, as a matter of fact Part I as here represented is in reality a second edition. Together with Part II, on the therapy of cancer, which is a hitherto unpublished addition, it forms the first appearance in book form of "Some Notes on Cancer."

In the somewhat brilliant Preface from which the foregoing excerpt is taken, the author continues "Personally the author rather rubs his eyes when he looks at the book. . . . "

He is probably not the only one to "rub his eyes when he looks at the book," for in the "Synopsis of the Contents" in page xxiii of the Introduction, the author explains the subject somewhat as follows:

"The great factor in the etiology of carcinoma is hyperalkalinity of the blood, which in itself may be harmless, but which in coöperation with chronic irritation in one with an inherited predisposition, by inducing weakness of the sympathetic nervous system results in disturbance of the physiologic equilibrium of the effects of the hormones of the pancreas and parathyroids, and disturbance of the acid-base reaction in which potassium becomes preponderant over calcium. On the basis of this hyperalkalinity, chronic irritation sets in motion the proliferative process of epithelial cells that constitutes cancer (or malignancy)."

"The confirmed observation that malignancy can develop only in the presence of alkalosis would seem to make acidosis appear as the obvious remedy.

"*An induced clinical acidosis to pH values below of what is normal for the patient in question will probably, as a rule cleanse his whole system permanently of everything pertaining to cancer, viz., susceptibility, tumor, disseminated cancer cells and metastases. It then definitely precludes recurrence.*"

Having preceded this far, the reader will no doubt recall the quotation from Faust that is given in the preface: "I am so bewildered by all this learning, as if in my head mill-wheels were turning," and begin to wonder whether to proceed or stop. If he does the former, he finds the remainder of the book to be made up of a somewhat wordy, though not unentertaining, series of argu-

ments in support of the general thesis given above, interwoven with a great collection of such excerpts from the literature as favor it, with complete neglect of everything to the contrary.

To those who happily emerge convinced that the author is correct in his deductions, the immediate application of the system is urged; for what more can be desired than the "permanent cleansing of the whole system of everything pertaining to cancer—susceptibility, tumor, disseminated cancer cells, metastasis and recurrence?"

J. McF.

BOOKS RECEIVED.

NEW BOOKS.

Guy's Hospital Reports, Vol. 81 (Vol. 2, Fourth Series) No. 1, January, 1931. Edited by ARTHUR F. HURST, M.D., Assisted by various contributors. Pp. 126. London: The Lancet, Ltd., 1931. Price, 12/6 net.

Sixty Centuries of Health and Physick. By S. G. BLAXLAND STUBBS and E. W. BLIGH. With an Introduction by SIR HUMPHRY ROLLESTON, BART, G.C.V.O., K.C.B., M.D., HON. D.C.L., LL.D., D.SC., Regius Professor of Physic in the University of Cambridge. Pp. 253; 101 illustrations, 1 colored. London: Sampson Low Marston & Co., Ltd., 1931. American Publisher: Paul B. Hoeber, Inc., New York. Price, 15s.

Primary Syphilis in the Female. By THOMAS ANWYL DAVIES, M.D., LOND., Director of the Whitechapel (L.C.C.) Clinic. Pp. 111. New York: Oxford University Press, 1931. Price, $4.00.

The Physician of the Dance of Death. By ALDRED SCOTT WARTHIN, PH.D., M.D., LL.D., Professor of Pathology and Director of the Pathological Laboratories in the University of Michigan, Ann Arbor. Pp. 142; 92 illustrations. New York: Paul B. Hoeber, Inc., 1931. Price, $7.50.

Crippled Children. Their Treatment and Orthopedic Nursing. By EARL D. MCBRIDE, B.S., M.D., F.A.C.S., Instructor in Orthopedic Surgery, University of Oklahoma, School of Medicine. Pp. 280; 159 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, $3.50.

Discovering Ourselves. By EDWARD A. STRECKER, A.M., M.D. and KENNETH E. APPEL, PH.D., M.D. Pp. 306; 28 illustrations. New York: The Macmillan Company, 1931. Price, $3.00.

Concerning the Origin of First Blood Corpuscle, First Blood Plasma, First Blood Space, First Bloodvessel. Origin of Cancer. By FRANK A. STAHL, M.D. Pp. 157; 95 illustrations. Chicago: By author, 1931.

The Letters of Dr. Betterman. By CHARLES ELTON BLANCHARD. Pp. 157. Youngstown, Ohio: Medical Success Press, 1931. Price, $1.00.

Studien uber die Entstehung und den Verlauf der Lungenkrankheiten. By DR. N. PH. TENDELOO, o.ö. Professor der Allgemeinen Pathologie und der Pathologischen Anatomie, Direktor des Pathologischen Instituts der Reichsuniversitat Leiden. Pp. 219; 6 illustrations. München: J. F. Bergmann, 1931. Price, R. M. 26.

The Physical Basis of Personality. By CHARLES R. STOCKARD, Professor of Anatomy and Director of the Anatomical Laboratories and the Experimental Morphology Farm in the Cornell University Medical College. Pp. 320; 73 illustrations. New York: W. W. Norton & Co., 1931. Price, $3.50.

Quantitative Clinical Chemistry, Vol. 1, Interpretations. By JOHN P. PETERS, M.D., M.A., Professor of Internal Medicine, Yale University School of Medicine, and DONALD D. VAN SLYKE, PH.D., SC.D., Member of The Rockefeller Institute for Medical Research. Pp. 1264; 124 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, $12.00.

Some Aspects of The Cancer Problem. Edited by W. BLAIR BELL, B.S., M.D., LOND., F.R.C.S., ENG., HON. F.A.C.S., Fellow of King's College, London; Director of the Liverpool Medical Research Organization. Pp. 543; 273 illustrations. New York: William Wood & Co., 1930. Price, $20.00.

Proteus, Band 1. Verhandlungsberichte der Rheinischen Gesellschaft für Geschichte der Naturwissenschaft, Medizin und Technik, mit Festgabe für Wilhelm Haberling. By PAUL DIERGART. Pp. 281. Bonn: Bonner Druck und Verlagsanstalt, L. Neuendorff, 1931.

Acta Societatis Medicorum Fennicæ "Duodecim," Ser. B., Vol. 13, No. 2. Pp. 205. Helsinki, 1931.

Most of this volume is taken up by an extended study of the normal blood *sugar* curve.

Oxford Monographs on Diagnosis and Treatment. Edited by HENRY A. CHRISTIAN, M.D., SC.D., LL.D. *Volume X. The Diagnosis and Treatment of Pneumonia.* By CAMPBELL P. HOWARD, B.A., M.D., C.M., F.R.C.P. and S. (CAN.), Professor of Medicine, McGill University, and Physician to the Montreal General Hospital. Pp. 263. New York: Oxford University Press, 1931.

Coal-miners' Nystagmus. By G. F. HAYCRAFT, M.R.C.S., L.R.C.P., D.O.M. and S. Pp. 15. New York: Oxford University Press, 1931. Price, 30¢.

Health at The Gateway. By. E. W. HOPE, O.B.E., M.D., D.Sc., Professor of Public Health, University of Liverpool, formerly Medical Officer of Health, City and Port of Liverpool. Pp. 213; illustrated. London: Cambridge University Press, 1931.

Surgery: A Hundred Years Ago. Extracts from the Diary of Dr. C. B. TILANUS, Afterward Professor of Surgery at the University of Amsterdam. Edited by PROFESSOR H. T. DEELMAN, Professor of Pathology at the University of Groningen, Holland. Translated from the Dutch by Joseph Bles. Pp. 156; illustrated. London: Geoffrey Bles, 1925. Price, 6s.

The Diet Book. By MARGUERITE REQUA REA, with a Foreword by SIR JAMES PURVES-STEWART, K.C.M.G., C.B., M.D. (ED.), F.R.C.P. (LONDON), Physician to Westminster Hospital. Pp. 197. New York: Oxford University Press, 1931. Price, $2.75.

A useful combination of dietary lists suitable for many diseases with recipes such as found in the usual cook-books.

The Diagnosis and Treatment of Brain Tumors. By ERNEST SACHS, A.B., M.D., Professor of Clinical Neurological Surgery, Washington University School of Medicine, St. Louis. Pp. 396; 224 illustrations 10 in colors. St. Louis: The C. V. Mosby Company, 1931. Price, $10.00.

Easier Motherhood. By CONSTANCE L. TODD. Pp. 199. New York: The John Day Company, 1931.

Transactions of the American Otological Society, Inc., Sixty-third Annual Meeting, Swampscott, Mass., May 20 and 21, 1930, Vol. XX. Pp. 299; illustrated. New Bedford, Mass.: The Society Reynolds Printing.

Lehrbuch der Allgemeinen Physiologie. By ERNST GELLHORN. Pp. 741; 126 illustrations. Leipzig: Georg Thieme, 1931. Price, M. 49.50.

NEW EDITIONS.

A Handbook for Senior Nurses and Midwives. By J. K. WATSON, M.D. (EDIN.), CAPT., R.A.M.C., Late House-Surgeon, Essex and Colchester Hospital. Pp. 676; 225 illustrations. Second edition. New York: Oxford University Press, 1931. Price, $4.00.

Recent Advances in Cardiology. By C. F. TERENCE EAST, M.A., M.D. (OXON.), F.R.C.P. (LOND.), Junior Physician, King's College Hospital, and C. W. Curtis Bain, M.C., M.B. (OXON.), M.R.C.P. (LOND)., Physician, Harrogate Infirmary. Pp. 353; 72 illustrations. Second edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1931. Price, $3.50.

We have but one criticism to make of these volumes of "Recent Advances" by British authors and that is the misleading quality of the title. Fortunately it is not interpreted strictly and instead of a disjointed description of recent advances only, we have the chinks filled in to make a useful modern presentation of the subject. Perhaps for the same reason the numerous pre-armistice references are desirable without implying chauvinism. There is a regrettable overemphasis of British authorities. E. K.

The Principles and Practice of Perimetry. By LUTHER C. PETER, A.M., M.D., Sc.D., F.A.C.S., Professor of Ophthalmology in the Graduate School of the University of Pennsylvania. Pp. 315; 199 illustrations. Third edition. Philadelphia: Lea & Febiger, 1931. Price, $4.50.

The third edition of this popular textbook contains the author's suggestions for recording fields by the anatomic method. The material has been brought up to date in nearly every phase of the subject. F. A.

Practical Dietetics in Health and Disease. By SANFORD BLUM, A.B., M.S., M.D., Head of Department of Pediatrics and Director of the Research Laboratory, San Francisco Polyclinic and Post-graduate School. Pp. 380. Fourth revised and enlarged edition. Philadelphia: F. A. Davis Company, 1931. Price, $4.00.

Hemorrhoids, The Injection Treatment and Pruritus Ani. By LAWRENCE GOLDBACHER, M.D., Philadelphia. Pp. 207; 31 illustrations. Second revised edition. Philadelphia: F. A. Davis Company, 1931. Price, $3.50.

This second edition of Goldbacher's monograph on hemorrhoids and their treatment by injection differs very little from the first. The anatomy, classification, symptoms of hemorrhoids are discussed and the author's method of the treatment of internal hemorrhoids by the injection of a 5 per cent oily solution of phenol is fully described with illustrative cases. Pruritus ani is also treated by subcutaneous injections of phenolized oil. L. F.

Der Elektrische Unfall. By DR. STEFAN JELLINEK, A. O. Professor der Elektropathologie an der Universitat Honorardozent an der Technischen Hochschule in Wien. Pp. 168; 50 illustrations. Third edition. Leipzig and Wien: Franz Deuticke, 1931. Price, 8 M. (12s.); 10 M. (15s.) bound.

Surgery. Its Principles and Practice. By ASTLEY PASTON COOPER ASHHURST, A.B., M.D., F.A.C.S., Professor of Clinical Surgery in the University of Pennsylvania. Pp. 1189; 1063 illustrations. Fourth edition thoroughly revised. Philadelphia: Lea & Febiger, 1931. Price, $10.00.

The Vitamins. Monograph Series No. 6. By H. C. SHERMAN, MITCHILL, Professor of Chemistry, Columbia University, and S. L. SMITH, Senior Chemist, Office of Experiment Stations, United States Department of Agriculture. Pp. 525. New York: The Chemical Catalog Company, Inc., 1931. Price, $6.00.

PROGRESS
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The Production of Acute Nephritis by Means of a Pneumococcal Autolysate.—BLACKMAN, BROWN and RAKE (*Bull. Johns Hopkins Hosp.*, 1931, **48**, 74) write that the problem of the production of nephritis in animals by means of a bacterial infection or bacterial products has occupied for some years the attention of many investigators, with results that have for the most part yielded little of definite information. In their present paper they report upon the changes comparable to acute and subacute nephritis of man produced in rabbits with an autolysate from pneumococci. Their human autopsy records show that in about 40 to 50 per cent of those dying from pneumococcal infection the lesions found in the kidneys often parallel those produced in rabbits. The streptococcus has been the organism that has been used by most investigators, but Duval and Hibbard have produced the changes of acute nephritis through the use of a streptococcal lysate prepared *in vivo* in the peritoneum of immunized animals. No work has been done, however, with the pneumococcus to attempt to incriminate it in the production of nephritis. The method employed by others to produce the autolysate is that described by Parker. After the completion of the technique, the sterility was proven by culture. In order to find out if the toxin of the autolysate might not come from the action of the disintegrated bacteria upon the broth contents rather than being an actual endotoxin, experiments were carried out in which the pneumococcus was allowed to autolyze in normal saline. This autolysate produced a skin reaction in guinea pigs and kidney lesions resembling in every way those obtained after injection of the broth autolysate. In the main experiments 44 rabbits were used, the autolysate being injected intravenously in variable doses ranging from 0.3 to 2.4 cc. with from 1 to 9 injections. Forty-one of their rabbits showed definite pathologic changes in their kidneys with involvement of the glomeruli or the tubules or both. Grossly, in the majority of cases the kidneys were swollen, edematous and of a pale yellow color, frequently with petechial hemorrhages on the surface. The lesions

microscopically affected generally the glomerular capillaries as shown by the presence of hyaline and fibrin thrombi, blood and fibrin in the tubules and necrosis of the epithelial glomeruli and tubules. In a certain number of instances there was quite marked edema and ascites. The bodies of the autopsied animals showed no alteration aside from the edema except in the voluntary and heart muscle. Twenty-four control animals were used and were given a veal peptone broth without changes being produced in the kidney. The work of these investigators was further enlarged by injecting a small series of rabbits with pneumococci intradermally. Somewhat over one-third of the animals injected showed the changes of subacute or acute nephritis. The clinician as a rule does not usually consider pneumonia likely to be complicated by nephritis, but these investigators have shown definitely that nephritis can be produced by the toxin of the pneumococcus.

SURGERY

UNDER THE CHARGE OF
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Undifferentiated Round-cell Sarcomas. — PHEMISTER (*Ann. Surg.*, 1931, **93**, 125) claims that the usual teaching in connection with malignant tumors is that the less differentiated the cell, the more malignant the tumor, the earlier it gives rise to metastases and the worse the prognosis. While this may be true for tumors in general, all four assumptions (classification of Broders) merit criticism for particular types of tumors. Sarcoma presents exceptions to the rule oftener than carcinoma and there is perhaps no better example than is offered by the undifferentiated round-cell sarcoma met with most frequently in connection with the bone and connective tissues of the soft parts of the extremities. Cures lasting from four and two-thirds to ten and three-fourths years, have been obtained in 5 cases of undifferentiated round-cell sarcomas, 2 of which began in bone and 3 in the connective tissues about bone. Biopsy performed in 4 cases, a pathologic fracture in 1 and a previous incomplete operation in 1, did not lead to metastases. This experience favors the view that biopsy is not a dangerous procedure. One tumor was treated by irradiation only, 1 by amputation and 3 by both irradiation and local excision. Several years were required in one case for sequestration of the bone killed by radium used in the treatment due to the fact that the adjacent tissues which produced the absorption were radium burnt.

Vaccination Against Peritonitis in Surgery of the Colon.—RANKIN and BARGEN (*Arch. Surg.*, 1931, **22**, 98) say that these studies emphasize the value of pre-operative protection against peritonitis in procedures in which resection of parts of the large intestine are involved. That the intraperitoneal vaccination is one of the major parts of the

preparation is demonstrated by the following facts: In the same week the same surgeon has operated on 2 patients of the same general build, age and otherwise offering a similar surgical risk, with lesions in identical situations, and has employed the same surgical maneuver, but 1 patient received vaccine and the other did not. The first patient died within five or six days from generalized peritonitis and the second made a smooth, uneventful recovery. Except for the vaccine the pre-operative measures in both cases were the same. It has been amply demonstrated that protection against lethal peritonitis can be established in animals. The relative transient nature of such immunity is noteworthy. The time element between vaccination and operation is important. That the logical preventive reagent is a vaccine, prepared from streptococci and colon bacilli, is suggested by the predominant presence of these organisms in the exudate in fatal cases of peritonitis and their vast predominance in and around malignant lesions of the large intestines. Future experimental work and the method of trial and error should establish the best reagent for this mechanism of protection against peritonitis.

THERAPEUTICS

UNDER THE CHARGE OF

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A Potent Liver Extract for Intramuscular Administration.—A highly potent, inexpensive liver extract suitable for intramuscular administration is reported by GÄNSSLEN (*Klin. Wchnschr.*, 1930, **8**, 2099). This preparation is obtained by squeezing out the juice from fresh raw liver hash under high pressure. The proteins are then precipitated by various procedures. The filtrate thus obtained is treated like any other preparation for intramuscular use. This extract is so potent that 2 cc. injected daily (the amount extracted from 5 gm. of fresh liver) is as active as 300 to 600 gm. of fresh liver. Thus the extract when injected is about fifty times more potent than liver administered by mouth. The potency of the extract is so high that a complete cure can be obtained with an amount of liver extract which is equivalent to a single daily dose of raw liver taken by mouth. Forty patients suffering from pernicious anemia were treated with the extract. The author usually administered 2 cc. of the extract intragluteally. The onset of the blood regeneration was not hastened when the daily dose was raised to 3 or 4 cc. Individual variations occurred. In the majority of instances the anemia disappeared within six to eight weeks. No failures were observed. It was repeatedly noticed that in the first

days of treatment the severity of the anemia increased. Aside from the effect of the extract on the blood, there was also a marked improvement of the appetite and a gain in weight. A number of the patients showed improvement of the symptoms and signs of combined system disease. A group of patients with secondary anemia also benefited from this treatment. The rise of the hemoglobin content in cases with secondary anemia occurred more slowly than in those with primary anemia. Experiments on animals as well as observations on patients indicate that the extract contains an active principle which influences the carbohydrate metabolism and reduces the glycogen content of the liver. The blood sugar is not reduced. Untoward reactions following the administration of the extract are not mentioned. The observations presented, if confirmed, are of considerable practical and theoretical significance.

The Beneficial Effects of Certain Placental Extracts.—The alcoholic extracts of the human placenta can be separated into three fractions, each possessing distinctive physiologic properties. CAMPBELL and COLLIP (*Brit. Med. J.*, 1930, p. 1081) now report the possible therapeutic value of the 85 per cent alcohol-soluble fraction, also called "emmenin." A few clinical observations on the so-called "anterior pituitary-like fraction of the placental extract," which is precipitated by 85 per cent alcohol, are also described. One hundred and twenty-three cases of deranged ovarian function were treated for three to nine months. All the patients studied were apparently normal and pelvic examination revealed no gross or obviously pathologic conditions of the uterus or its adnexa. The authors refrain from drawing final conclusions as to the possible therapeutic value of the extract. The effect of emmenin was particularly encouraging in the group with dysmenorrhea. It is suggestive that it corrected certain types of amenorrhea of recent origin. It definitely lengthened cycles in polymenorrhea. It frequently relieved menopausal symptoms of recent origin, but did not relieve symptoms in castrates. Emmenin did not alter normal menstrual cycles. The equivalent of 75 gm. of placenta in divided doses given daily in water and orange juice before meals was used in a majority of cases. Some of the individuals did not tolerate the extract well, developing nausea and vertigo. The dose for such individuals was reduced. Impregnation and gestation were uninfluenced. Four patients became pregnant while receiving emmenin for ovarian dysfunction. Some patients volunteered the information that thirty-six to forty-eight hours after the onset of therapy they experienced a sensation of well-being and mental alertness. No effect on the libido was reported. The dosage used in dysmenorrhea was usually the equivalent of 25 gm. of placenta administered daily beginning with the cessation of the menstrual period. During the week preceding menstruation the dose was raised to 75 gm. daily. This dose was continued until the onset of the flow. In 5 cases with metrorrhagia, the "anterior pituitary-like substance of placenta," in amounts equivalent to ten rat units per cubic centimeter, was administered subcutaneously. The therapeutic results were encouraging.

PEDIATRICS

UNDER THE CHARGE OF

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The Periodical Recurrent Incidence of Respiratory Infections in Early Childhood.—McLEAN (*Arch. Pediat.*, 1931, **48**, 145) states that various investigators have shown that climatic conditions, geographic location and personal hygiene of individuals apparently have little effect on their susceptibility to repeated attacks of respiratory infections. This investigation showed that recurrent respiratory infections are common in children of all ages and occur in about the same percentage of cases each year. Weather conditions, removal of tonsils and adenoids and contact with other individuals with the disease did not seem to influence the number of recurrent respiratory infections. In an analysis of the records of 582 children observed, between September 1, 1925, and June 1, 1930, it was found that 78 per cent of the children had one or more recurrent respiratory infections each year of observation. In the 22 per cent of the cases in which the records show no recurrent infections the majority were either transient patients or cases seen only during the acute illness of the primary infection. The average number of recurrent respiratory infections per patient, according to length of observation and age grouping, showed a marked consistency. Thirty-four patients observed 1739 months, over a period of from 4 to 5 years, had 232 recurrent respiratory infections. The average number of months per recurrent infection in patients of all ages was 7.4 months; the children younger than 1 year, when seen with the primary infection, averaging 7.5, those between 1 and 2 years, 7, and those over 2 years, 7.6 months. The season in the year in which patients were seen with the primary respiratory infection apparently had little or no influence of the number of recurrent respiratory infections. The author feels that the consistency in the periodical recurrent incidence in respiratory infections is more than suggestive of a periodical recurrent disease.

Tetany, Generalized Edema and Cerebral Compression in the Newborn.—SHANNON (*Arch. Pediat.*, 1931, **48**, 153) says that tetany is to be thought of as a symptom complex and not as a disease, due to a deficiency more qualitative than quantitative in the calcium content of the blood and tissues. It manifests itself primarily by a condition of increased irritability of nervous tissues, the symptoms varying according to the various nervous tissues most involved. Most characteristic are the motor symptoms by which it has been usually recognized. It has been recognized generally as occurring at all ages except during the neonatal period. For some reason this age period has been assumed to be exempt. It is contended that tetany is in reality of frequent occurrence in the newborn infant. This contention is supported by a

series of 9 cases presented, in 8 of which the usual manifestations of this symptom complex yielded rapidly to specific calcium therapy. In the one exception death occurred before therapy could have been expected to have any effect. Therapy consisted of calcium feeding, the administration of parathyroid extract and the use of viosterol. As additional evidence of the existence of calcium deficiency in these cases there is cited a generalized and definite edema which occurred in 8 of the 9 cases. In the ninth case, while no clinical edema occurred, a marked gain in weight was observed concomitant with the onset of symptoms. In all but 1, which was the fatal case, the symptoms of edema disappeared promptly under specific calcium therapy just as the nervous symptoms disappeared. In 7 of the 9 cases definite symptoms of cerebral compression accompanied the nervous symptoms and the edema. In all except the 1 fatal case the symptoms of cerebral compression disappeared promptly, along with those of nervous irritability and generalized edema under specific calcium therapy. In the fatal case death occurred within 1 hour of the administration of parathyroid extract, a period too short for a result to have been expected, and it occurred in a cyanotic spell which resulted, as shown by the postmortem, from cerebral compression due to a tremendous edema of the brain. It is, therefore, further contended that, standing in a causal relationship with the tetany, which is of frequent occurrence in the newborn, there exist two groups of symptoms dependent also upon the deficiency in calcium, general subcutaneous edema, edema of the brain and the three groups form a triad dependent primarily upon a quantitative or qualitative deficiency in the calcium metabolism of the newborn. It is observed that all three groups of symptoms respond readily to specific therapy directed at correcting a deficiency in the calcium of the blood and tissues. The possible rôle of salts other than calcium, such as magnesium, sodium and potassium, is recognized but believed to be minor to that of calcium because of the profound effects of the latter salt upon the triad of symptoms.

Purpura Hemorrhagica (Thrombocytopenia).—DeSanctis and Allen (*Am. J. Dis. Child.*, 1931, **41**, 552) report 3 cases of thrombocytopenia. The chief complaint and outstanding symptom in the 3 cases was a persistent and uncontrollable nosebleed. The observations on the blood were typical. There was a marked thrombocytopenia, that is, a reduction in the blood platelets, normal coagulation time, normal bleeding time and a nonretractile clot. Splenectomy was performed in 3 cases. The pathologic diagnosis from examination of the removed spleens was a fibrosis of that organ. In 2 of the 3 cases there was no recurrence of the bleeding after the operation. In 1 case there were several recurrences of epistaxis and petechiæ after the operation, although they were easily controlled. The rapid destruction of the platelets is due to factors activating the reticuloendothelial system to unusual thrombocytolytic action. The recurrence of bleeding in splenectomized persons seemed to indicate that, although a large portion of the reticuloendothelial system had been removed by the operation, the remainder has probably been activated to renewed activity of platelet destruction by the activating factor, whatever that is.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Pyoderma (Ecthyma) Gangrenosum.—Brunsting, Goeckermann and O'Leary (*Arch. Dermat. and Syph.*, 1930, **22**, 655) discuss, on the basis of 5 cases, an unusual, extensive type of ulceration of the skin, in which the subjects were debilitated by reason of some infectious process elsewhere in the body. One had a chronic empyema and the other 4 were victims of chronic ulcerative colitis of years' standing. A striking parallel relationship was demonstrated between the activity of the cutaneous lesions and the major infectious focus, the intestines. The resemblance of the process to Amœbiasis cutis and hemolytic streptococcus gangrene of the skin is discussed. While no amœbæ were found, hemolytic streptococci and staphylococci appeared with consistent regularity in the secretion of the ulcer and in the deeper tissues of specimens removed for biopsy. Intradermal inoculation of rabbits with a combination of the foregoing organisms produced an ulcerative area similar to the undermining lesions seen in the patients. The authors believe that the cutaneous picture is simply one part of a generalized infectious syndrome. Healing of the cutaneous lesions is dependent on the successful treatment of the systemic disease.

Explanation of the Mechanism of the Wassermann and Precipitation Tests for Syphilis.—Eagle (*Bull. Johns Hopkins Hosp.*, 1930, **47**, 292) believes that flocculation tests for syphilis and bacterial agglutination by an antiserum as well as the Bordet-Gengou phenomenon of the Wassermann test are due to identical underlying basic mechanisms. Reagin and altered globulin in syphilitic serum combine with the colloidal particles of beef-heart lipoid ("antigen"). The surface film of protein thus formed sensitizes the particles to flocculation by electrolyte and also adsorbs complement. Antibody globulin affects bacteria, red cells or foreign protein in exactly the same manner. The author believes, therefore, that the serum change characteristic of syphilis may well represent an antibody response to products of infection. In another publication (*J. Exper. Med.*, 1930, **52**, 747) the author explains the mechanism of the action of cholesterin as a fortifying agent in the Wassermann and flocculation tests. He finds that when a cholesterinized antigen is dropped into an excess of water, the rapid flocculation of cholesterin crystals is prevented by the fact that as tiny particles or aggregates form they adsorb a protective surface of the antigen

which is really a hydrophilic lecithin. This prevents further aggregation, and gives the suspension stable properties. Apparently cholesterin, when added to antigen for fortifying purposes, markedly coarsens the character of the lecithin suspension, thus creating larger nuclei upon which the subsequently added antigen is adsorbed. The author has also apparently shown that the larger the antigen particle, the greater is its avidity for reagin per unit surface or mass. Cholesterin, therefore, increases the sensitivity of antigen to the syphilitic reagin by coarsening the dispersion of the particles in the antigen suspension. By increasing the concentration of cholesterin, or preferably, since this is somewhat difficult, by selecting other agents than cholesterin to secure the same physical effect, it should be possible to increase enormously the sensitivity of antigens in the Wassermann and precipitation tests without necessarily impairing their clinical validity on the score of nonspecificity.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Pregnancy After Radium Cure of Uterine Carcinoma.—In reporting the birth of a living child after irradiation of a carcinoma of the cervix before the Obstetrical and Gynecological Society of Berlin, PHILIPP (*Centralbl. f. Gynäk.*, 1931, **55**, 309) states that such an event is exceedingly rare. In 1924 a forty-two-year-old patient came to his clinic showing a carcinoma of the cervix and at the same time was four months pregnant. The carcinoma was of the ulcerative type and extended to the vaginal mucosa although the parametria were not involved. Microscopy confirmed the diagnosis of carcinoma. Bacterial examination of the growth showed the presence of highly virulent streptococci on account of which an operation was considered as attended by too great a mortality, and irradiation was decided upon. With the hope of allowing the pregnancy to continue, the radium was so placed in the cervical canal that the gestation sac was not touched. A dose of 118 mg. of radium was given for thirty hours, which was repeated in nine days so that the total dosage was about 7000 mg. hours. Although the pregnancy continued, she aborted two and a half months later. After the abortion she did not menstruate for nine months, then the menses again appeared and were perfectly regular every four weeks and about as profuse as before the irradiation. She became pregnant in 1926, and on February 28, 1927, she gave birth to a female child. This labor was longer than her previous ones but was without complications. Her periods returned six months after delivery and have continued to date. Examination at the time of the report showed the cervix shrunken, the vaginal fornices consider-

ably shortened, the uterus small and anteflexed and she felt extraordinarily well. The child is also apparently perfectly healthy. Philipp emphasizes that this patient never was subjected to Roentgen irradiation. The fact that she aborted the pregnancy that was present at the time of the radium treatment is not unusual, since the ovarian influence is of great importance in the retention of an early pregnancy. He states that the literature shows that irradiation during the first half of pregnancy is usually promptly followed by abortion, whereas irradiation during the second half of pregnancy may have no effect and the gestation may go to term. This case proves that radium can cure a carcinoma of the cervix and at the same time preserve the future function of both the uterus and the ovaries. This case confirms the statements which have been made by Douglas P. Murphy, of the Gynecean Hospital Institute of Gynecological Research of the University of Pennsylvania, to the effect that preconception therapeutic irradiation by either radium or Roentgen ray is harmless to subsequent pregnancies. The latter authority has amply demonstrated, however, the dangers to the child of postconception therapeutic irradiation. If abortion does not follow the latter types of irradiation the child is prone to be deformed and is often a microcephalic idiot.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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The Differentiation and Significance of Certain Ophthalmoscopic Pictures in Hypertensive Disease.—FISHBERG and OPPENHEIMER (*Arch. Int. Med.*, 1930, **46**, 901) believe that the retinal changes occurring in patients with arterial hypertension can be differentiated into three types: (1) Retinal arteriosclerosis and arteriosclerotic retinopathy. (2) Malignant hypertensive neuroretinitis; and (3) choked disk due to increased intracranial pressure. The first type, arteriosclerosis with or without hemorrhages and punctate exudates, but without cotton-wool patches or edema of the disk, is found usually in essential hypertension but also in long-standing glomerulonephritis. Its significance is purely that of arteriosclerosis. The patients die, often after many years, from cardiac failure, coronary closures, or cerebral vascular disease—seldom from renal insufficiency. Malignant hypertensive neuroretinitis is of much more ominous prognostic significance. It occurs in glomerulonephritis, essential hypertension and in the toxemia of pregnancy. It is characterized especially by edema of the disks, marked narrowing of the arteries, and cotton-wool patches and hemorrhages in the retina. The amount of arteriosclerosis present depends upon the previous duration of the hypertension. For the explanation of its pathogenesis, Volhard's theory of ischemia of the retina from spastic contraction of the retinal arteries seems most sati-

factory. Most of these cases go on to renal insufficiency and uremia. Necrosis of the renal arterioles is found at necropsy in cases of essential hypertensive neuroretinitis, but not in glomerulonephritis. Choked disk due to edema of the brain is seen in glomerulonephritis, but not in essential hypertension. It does not indicate oncoming renal insufficiency and its prognostic significance is not necessarily bad. In 27 cases of acute and subacute glomerulonephritis, malignant hypertensive neuroretinitis was found in 1 patient. He died within two months. Choked disk ducts and edema of the brain occurred in one patient. In 8 patients slight constriction of the arteries or slight haziness of the disks was seen. These changes and the presence of a few small hemorrhages have no especial prognostic significance. Of 55 cases of chronic glomerulonephritis, the fundus was negative in 24; 5 of these patients died while in the hospital. Retinal arteriosclerosis only was found in 8, none of whom died. Arteriosclerotic retinopathy was present in 6, 3 of whom died. In these the glomerulonephritis was accompanied by arteriosclerosis. Malignant hypertensive neuroretinitis was found in 17, 11 of whom died in uremia. Of 189 cases of essential hypertension, the fundus was negative in 13, one of whom died of cerebral hemorrhage. Renal function was normal in all. Marked narrowing of the arteries was present alone in 11, 9 of whom had normal renal function and none of whom died. Retinal arteriosclerosis alone was found in 70; 57 had normal renal function, and 9 died. Arteriosclerotic retinopathy was present in 58; 37 had normal renal function, 5 died. Malignant hypertensive neuroretinitis was found in 37, 11 had normal renal functions, and 13 died. Eighty-four per cent of the entire group had retinal arteriosclerosis, which indicates that the hypertension had probably been present for a considerable time. Most of them had evidences of arteriosclerotic disease in other organs, especially the heart and brain; but they may get on well for years. Malignant hypertensive neuroretinitis may appear at any stage of essential hypertension, but it affects especially the younger age groups. Twenty-six of the 37 patients were between the ages of thirty and forty-nine years. The progress of impairment of renal function is rapid, due to the onset of neurosis of the renal arterioles, the "malignant sclerosis" of Fahr, which is not present in cases of essential hypertension without the malignant type of retinitis and which probably develops after the onset of the retinitis. The prognosis is grave. In one of the patients who died the hypertension was due to suprarenal tumors. In one patient who died in uremia from amyloid kidneys of long standing, hypertension and arteriosclerotic retinopathy were present. However, the vast majority of patients with amyloid disease of the kidneys have normal retinas.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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Rhinosporidium Seeberi: Pathological History and Report of the Third Case from the United States.—The infectious diseases of human beings, some probably beginning in their animal ancestors and com-

municated to primitive man, developed under environmental conditions analogous to animal life. While many of the factors formerly operative in placing infections constantly within the reach of mankind have been eliminated, others have supplanted them so that even today the animal acts as the reservoir for many infectious agents capable of producing disease in human tissues. Just as everything in Nature is constantly changing, so under the varying conditions of civilization long-forgotten maladies may reappear in old or new guises. No stronger proof can be found that there is still much to be learned concerning parasitic microörganisms, comparatively and experimentally, as well as concerning the natural history of infectious diseases, than in the recent outbreaks of tularemia, undulant fever and psittacosis. And now our attention is directed to human infection by Rhinosporidium seeberi by WELLER and RIKER (*Am. J. Path.*, 1930, **6**, 721). Accepting Ashworth's assignment of this organism to a systematic position among the lower fungi, the authors, in reporting the clinical and histopathological findings of a man, aged twenty-six years, comprehensively review the historical, etiologic, symptomatological and therapeutic phases of this rare condition. High points are: (1) Rarity (*circa* 40 cases); (2) discontinuous geographic distribution (India and Ceylon; Argentine (3 cases); United States (3 cases)); (3) apparent selectivity for males; (4) not necessarily confined to nose and nasopharynx (aural canal, conjunctiva, uvula, penis); (5) polypoid or papillomatous nature with tendency to bleed; (6) characteristic doubly-contoured parasitic cysts, each a single organism, in various stages of development; and (7) likelihood of recurrence, especially following incomplete surgical removal.

RADIOLOGY

UNDER THE CHARGE OF

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The Site of Predilection in Cross-infection from the Right to the Left Lung.—Infections of the right lung which result in destruction of pulmonary tissue not infrequently give rise to infection in the opposite lung. This is termed "cross infection" by COLE and his associates (*Radiology*, 1930, **15**, 627). They consider it an autogenous infection due apparently to the inhalation of infectious exudate and detritus. Although cross infection of this type may occur in any part of the left lung, there is such a tendency for it to occur in a region midway between the apex and base that this can be considered the site of predilection. In roentgenograms made in the usual postero-anterior projection this area lies between the second and fifth ribs. The entire area may be involved but usually the focus, if early, will be limited. When a destructive lesion involves particularly the right upper lobe one would expect aspiration infection of the right lower lobe to precede cross infection.

for the bronchus to the right lower lobe is an almost direct continuation of the trachea. This type of secondary infection does occur, usually in association with cross infection, but is most often limited to the peribronchial tissues. In certain cases, however, secondary infection of the lower lobe is more extensive than the cross infection. The authors present numerous roentgenograms illustrative of cross infection in tuberculosis and bronchopneumonia.

Intravenous Pyelography.—The indications for intravenous pyelography with uroselectan are listed by VON LICHTENBERG (*Radiology*, 1930, **15**, 664) as follows: (1) In those cases in which cystoscopy, catherization of the ureter and instrumental pyelography cannot be performed because of anatomic, pathologic or technical reasons. (2) In all cases of ureteral obstruction in which the contrast substance introduced by means of instrumental pyelography does not pass the point of obstruction. (3) In those cases in which instrumental pyelography cannot be undertaken without risk to the patient. To this group belong those patients whom one wishes to spare the pain of catheterization and of whose condition one can obtain sufficient information through intravenous pyelography. Specifically, the intravenous methods is applicable in patients suffering from stricture, severe bladder affections, hemorrhage, fistula, and in small children. It is applicable likewise in cases in which one hesitates to use the catheter, that is, in acute and chronic inflammatory infections of the adnexa, in tuberculosis and in cases of prostatic hypertrophy. A diagnostic film can be expected only in cases in which renal function is present, and the density of the shadow is dependent on the amount of function that exists. In severe bilateral infections of the kidneys, particularly those conditions associated with a damaged purulent parenchyma, the shadow will be absent, faint or considerably delayed.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Etiology of the Common Cold.—The feeling that the etiology of acute upper respiratory infections is extremely complicated has not prevented the earnest search for a single etiologic agent which might possibly lend itself to some specific means of control. LONG and DOULL (*Proc. Soc. Exper. Biol. and Med.*, 1930, **28**, 53) bring evidence that this agent is a filtrable virus. They were able to produce acute colds with bacteria-free Seitz or Berkefeld W filtrates of nasopharyngeal washings from persons with acute colds in 9 of 15 individuals inoculated, and

also obtained positive results by serial transfers through 2 and 4 individuals by the same method. (In the opinion of the retrospector these results only suggest that a preparation has been obtained by filtration sufficiently irritating to overwork the mucous membrane to a point at which the phenomena of the common cold developed). FROST (*Am. J. Pub. Health*, 1930, **20**, 843) has ably discussed the elusive features in the epidemiology of the common cold and emphasized that the problem being primarily one of identifying a pathologic process, the most urgent need seems to be a more intensive clinical study of the general family of minor respiratory diseases.

Seasonal Variation in Intestinal Flora.—The fact that many diseases vary in incidence and severity with the seasons has long been noted, and much work has been done to determine the factors involved. In intestinal infections this variation is particularly striking, and the view has seemed inevitable that there occurs a modification of the environment within the host favoring the particular microbes. GOLDWASSER and KLIGLER (*J. Prev. Med.*, 1930, **4**, 361) studied 117 stools from 12 normal individuals in Palestine over a twenty-month period and found a seasonal variation both quantitative and qualitative in the fecal flora. In winter the number of bacteria is relatively low, with cocci and anaërobic spore formers predominating. About April or May there is a transformation, the total number of bacteria falling and coli organisms are in excess. The coli-cocci ratio followed closely that of bacillary dysentery in the country, and suggested a factor favoring the development of these bacteria. A clear relation of their results to typhoid infection was not found and they suggest that typhoid may really be a glandular and not an intestinal infection.

HYGIENE AND PUBLIC HEALTH

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Studies in the Common Cold: IV. Experimental Transmission of the Common Cold to Anthropoid Apes and Human Beings by Means of a Filtrable Agent.—DOCHEZ, SHIBLEY and MILLS (*J. Exper. Med.*, 1930, **52**, 701) have found that chimpanzees would seem to be unusually satisfactory animals for use in the study of infection of the human upper respiratory tract. When they contract these infections the clinical picture they present is strikingly similar to that observed in man. This taken together with the fact that their bacteriologic flora is essentially like that of man suggests that their pathologic and im-

munologic response to bacteria pathogenic for the human upper respiratory tract may be sufficiently similar to make them the ideal experimental animal for this type of study. The tractability and coöperativeness of the chimpanzees makes them still more desirable. When well cared for they seem to keep in good health for long periods of time. Colds may be transmitted to man and chimpanzee by intranasal inoculation of filtered nasal washings. These filtrates usually can be shown to contain anaërobic filter passers of the type first described by Olitsky and Gates. However, evidence so far points to the probable nonpathogenicity of these organisms for man. That specific types in this group may be shown later to play a part in causing colds has been pointed out. If, however, as seems most probable at present, proof of this is not forthcoming, it follows that the active agent present in these filtrates, by which it has been possible to transmit colds, is a true submicroscopic virus. The sudden and plentiful appearance of pneumococci in the noses and throats of the chimpanzees in the course of colds has been most striking. The nature of this response is difficult of interpretation. There is little doubt that these organisms have been present before the infection, spontaneous or experimental, of the animal. They have been noted often in small numbers at various intervals in the throats of the animals and might well be shown to be regularly present by the mouse-injection method. Their prominence may well be the result of multiplication and spread upon a substrate of primary injury due to the filtrable agent or there may be some sort of activation of these potential pathogens by this agent. A like explanation may be offered for the spread to the nose of Bacillus pfeifferi and hemolytic streptococci.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF APRIL 20, 1931

Experiments on the Hydrolysis of Acetyl Cholin and Related Substances.—ANDRÉ SIMONART (from the laboratory of Pharmacology, University of Pennsylvania). The specificity of the ferment which splits acetyl cholin has been tested by examining the rate of destruction of two other esters of cholin very closely related chemically to acetyl cholin, *viz.*, propionyl and butyryl cholin. The rate of hydrolysis by diluted serum was followed on the blood pressure of a cat under ether anesthesia. The result has shown that the hydrolysis of all three esters of cholin is completed in the same length of time. The same experiment has been performed on two esters of slightly modified cholins, *viz.*, acetyl beta methyl cholin and acetyl gamma homocholin. The comparison between the rate of destruction of these compounds and that of acetyl cholin has shown that acetyl cholin is destroyed twice as quickly as acetyl gamma homocholin and nearly six times as quickly as acetyl beta methyl cholin. Eserin has been found to exert a very strong inhibition upon the hydrolysis of propionyl and butyryl

cholin. This is another property that is common to the splitting of all three cholin esters. These experiments make it very probable that the enzyme splitting acetyl cholin is not specific, but acts also upon other esters of cholin.

The ferment causing the hydrolysis of acetyl cholin and of other esters of cholin is supposed to belong to the important group of lipases and esterases. In the present state of knowledge of these enzymes this is difficult to determine definitely. A few arguments in favor of such a conception have been given by ENGELHART and LOEWI (*Arch. f. exp. Path. u. Pharm.*, 1930, **150,** 1), PLATTNER and HINTNER (*Pflüger's Arch.*, 1930, **225,** 19) and also by MATTHES (*J. Physiol.*, 1930, **70,** 338). Some further evidence is furnished by the following experiments made on the splitting of cholin esters and of triacetin, a simple ester unrelated to the cholins: Several extracts of different fetuses have been made to find out if it is possible to obtain an extract capable of splitting triacetin and not the cholin esters, or the reverse. These attempts have proved to be futile: by all of the examined extracts both triacetin and the cholin esters were hydrolyzed. According to HANRIOT (*Arch. d. Physiol.*, 1898, p. 797), lobster blood contains no esterase; tested for its power of splitting acetyl cholin, it has proved to be entirely lacking in such activity. The influence of eserin has been tested on the hydrolysis of triacetin: it was found that eserin inhibits this splitting, though far less powerfully than in the case of the cholin esters. The inhibition which is exerted by bile upon the activity of these enzymes has been found to extend to the splitting of triacetin as well as to that of the cholin esters.

For all those reasons it seems justifiable to consider the ferment which splits cholin esters as a member of the group of the esterases.

The Study of Protective Protein Films on Single Emulsion Droplets.—R. L. NUGENT (from the Gladwyne Research Laboratory, Gladwyne, Pa., and the Department of Industrial Research, University of Pennsylvania). At the present time it is quite generally agreed that emulsifying agents act by being adsorbed in the oil-water interface. In this way protective films are formed around the dispersed droplets which prevent their coalescence, and thus stabilize the emulsion. Proteins, soaps and gums are typical emulsifying agents. The experiments described in this paper deal with protein films on oil-in-water emulsion droplets.

In the past the investigation of the relative efficiencies of different emulsifying agents and of the same emulsifying agent under different conditions has been almost entirely on the basis of the relative ease of emulsification or the relative stability of the formed emulsion in the several cases. According to the adsorption film theory, the properties of the films on single droplets are the important factors. Therefore, the direct study of these properties would be expected to yield interesting information with regard to emulsification and protective action. This information should be of biologic value because of its application to clearcut biologic emulsions such as milk and blood plasma when it contains chylomicrons, and because any added information with regard to the surface films of protein is potentially applicable in the study of the surfaces of living cells.

Microcataphoretic experiments which have been performed by a number of workers, and those done in connection with the present paper, show that surface films of protein exhibit the electrokinetic properties characteristic of the protein of which they consist. Thus, they are isoelectric at the isoelectric point of this protein. These results are in accord with the use of the cataphoretic isoelectric point determination in studying the nature of the surfaces of living cells.

The Mudd interfacial technique seemed to offer a valuable method for the investigation of additional properties of protective protein films on single oil-in-water emulsion droplets, such as their state of hydration and their resistance to disruption under the action of interfacial and simple mechanical forces. This has been found to be the case on the basis of the study of the interfacial behavior of droplets of olive oil, with protective films respectively of gelatin and egg albumen and of fat droplets from cream. The examination of the behavior of each of the three types was made at a series of pH values.

The various types of behavior observed have been described and interpreted.

Under several conditions striking confirmatory evidence is afforded for the correctness of the adsorption film theory of emulsion stability.

The relative stabilities of a series of emulsions are shown to be predictable from the study of the properties of the films on single droplets.

It has been found possible to differentiate experimentally between two important protective properties of protein films, their resistance to disruption under the action of interfacial and mechanical forces and their hydration *per se*.

Finally, the state of hydration of protective films of a protein has been shown to vary with pH in the same manner as does the state of hydration of that protein in solution.

The Viscosity and the Wetting Properties of Leukocytes and Erythrocytes.—Emily B. H. Mudd and Stuart Mudd (from the Henry Phipps Institute, University of Pennsylvania). From a physical-chemical point of view, phagocytosis is a special case of spreading, the spreading of the phagocyte over the surface of the particle being ingested. In the body phagocytosis is enormously augmented by the deposit of serum proteins on the particle surface, and it is proving possible to define with some exactness the characteristics of the surface thus formed on the particle which produces a maximal tendency to phagocytosis.[1] In this work the interfacial technique has been applied to a study of the spreading surface, the surface of the leukocyte.

All leukocytes studied have a delicate, mobile surface membrane which is markedly hydrophilic. The average polymorphonuclear leukocyte is a less viscous cell than the mononuclear leukocyte, at least in the rabbit. Lymphocytes and leukemic leukocytes have seemed to be intermediate in viscosity between the rabbit polymorphonuclear and mononuclear leukocyte.

The erythrocyte possesses a surface membrane capable of being folded and of withstanding tension in the interface. The red cell surface

[1] Mudd, S., Lucké, B., McCutcheon, M., and Strumia, M.: J. Exper. Med., 1930, 52, 313.

is relatively hydrophobic. Evidence indicating that the erythrocyte surface contains both lipoid and protein components has been summarized in earlier papers.[1]

Identification of the Excitable Substances in Muscle.—W. A. H. Rushton (from the Johnson Foundation for Medical Physics, University of Pennsylvania). The communication was a summary of the past two years' work upon the question of the isochronism of muscle and nerve. Lucas' observations were confirmed in that there are two excitable substances in muscle, and various criteria were applied to show that the results are not due to experimental error. The two excitabilities are found in the spinal animal with nervous and circulatory systems intact, and other experiments were mentioned which make it unlikely that the duality was due to abnormal conditions. The α-excitability was shown to be supplied by nerves in spite of a difference in chronaxie in the ratio 1 to 100, hence isochronism cannot be essential for conduction. The two excitabilities were found in a dozen different muscles from various parts of the frog.

The two substances were identified by combining histologic and physiologic evidence to show that the γ-substance exists in the sartorius in the form of fibers apparently absent from the pelvic (nonneural) end, running in various directions, and terminating at the point of entry of the nerve trunk. These fibers are, therefore, nerve fibers and have the same chronaxie. The α-fibers have all the properties of muscle fibers and have a very great chronaxie. Isochronism is, therefore, only between nerve and nerve twigs, and not between nerve and muscle. Curare and fatigue by nerve tetanization act identially by leaving the α-excitability unaffected, and abolishing the γ-excitability. This is in complete accord with the foregoing, but quite incompatible with Lapicque's theory of curarization.

[1] J. Exper. Med., 1926, **43**, 127. Bechhold, H.: München. med. Wchnschr. 1921. **68**, 127.

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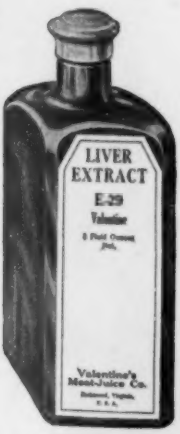

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